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THE CLINICAL SIGNIFICANCE AND APPLICATION OF HISTOLOGIC GRADING OF CANCERS

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The practicability, reliability and clinical significance of histologic grading of malignant tumors have been, in recent years, the subject of lively controversy among pathologists and clinicians engaged in the diagnosis and treatment of cancers. While numerous workers have adopted this method as a matter of routine and are using it extensively and successfully (Broders, Ewing, Hueper,[3] Martzloff, Greenough, Warren[8] and others) attaching to its results definite clinical significance, others have voiced scepticism in regard to its practical value (Wood[6]) or even condemn it as pure guess-work, being the product of a misconception and unreliable and even misleading in its results (Reimann[7]). As the danger exists that this discrepancy in the estimation of the merits of the method of grading is apt to cause confusion in the minds of those less familiar with this subject and with the issue at stake, and as the method of histologic grading may get into discredit through faulty technic and incorrect interpretation and application of the results obtained, as well as by unfounded criticism, it seems to be timely to present here a brief discussion of this subject.

I. *The reliability of the method from a purely pathologic standpoint depends upon the following factors.*—(1) The sections submitted for grading must originate from the peripheral, actively proliferating and therefore most characteristic portions of the tumor. Sections from ulcerated and infected parts, containing infections, nonspecific necroses and structural distorsions of the tumor structure, are less suitable for this purpose, while sections from the central, degenerating parts of the tumor with secondary fibrosis and necrosis are often misrepresentative of the actual type of growth and therefore objectionable for grading.

(2) The sections must contain a sufficient amount of tumor tissue to allow a fair and intelligent evaluation of the histologic structure of the tumor. As the cancer diagnosis is not a single-cell problem, but based upon the interpretation of the general cellular structure and arrangement of the tumor parenchyma and its relation to the surrounding stroma, there is a lower limit to the size of the section from which a diagnosis can reliably be made. It is, however, advisable not to use too small a piece of tissue for grading, even if it may suffice for diagnostic purposes.

(3) The presence of artificial cellular distorsions resulting from technical defects due to improper handling before fixation (drying, decomposition) or due to faulty preparation (fixation, dehydration) and staining, make sections unsuited for the method of histologic grading.

(4) The pathologist or whoever acts in this capacity must be familiar with the histopathology of tumors and especially with this type of work. It requires special training before that degree of experience is acquired in the structural analysis of tumors which is necessary for the proper grouping of tumors into grades of malignancy.

If any one of the above-mentioned basic requirements for the histologic grading of cancers is not fulfilled, the pathologist should not hesitate to refuse a request for a histologic malignancy determination, because results obtained without consideration of these factors are apt to be unreliable; and may thereby discredit a method which has its definite merits, if correctly performed and sensibly applied. Neglect of these technical rules is the cause of many of the discrepancies in the results obtained as reported by different authors. A good part of the criticism to which the method of histologic grading of cancers has been subjected in the past finds thereby a just and ready explanation.

Another source to which much of the criticism of the method of histologic grading can be traced may be found in the fact that the purpose of grading has been misunderstood and the results obtained have been applied without discrimination in regard to the character of the case and without consideration of the natural limitations of the method and the information gained through it.

The purpose of the histologic malignancy determination of cancers is an estimation of the potential proliferative qualities and metastatic tendencies of the neoplasm examined, through an evaluation of the degree of differentiation and amount of anaplasia presented by the tumor. The variations of these factors observed in the different cancers serve as the basis for their grouping into three or four grades of malignancy depending upon the technic employed by the different investigators. The histologically least malignant tumors receive grade 1. Cancers with histologic features indicating a higher degree of malignancy are graded accordingly into cancers of grade 2, 3 and 4. Consideration of the condition of the stroma is given only in the method of the histologic malignancy index as developed by Hueper. In all other methods, the interpretation of the histologic structure of the cancer is restricted to that of the parenchyma. An additional difference between the methods of this latter type and that of the histologic malignancy index is found in the technic of evaluation employed. While the investigators, following more or less closely Broder's lead, grade mainly on the basis of a general impression, that is, according to the percentage of the undifferentiated cells present in the tumor, Hueper's method is based on a numerical evaluation of twenty different histologic factors pertaining to the tumor parenchyma as well as to the stroma.

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Considering the fact that surgery as well as X-ray and radium therapy are mainly local means for the eradication of cancers and are only successfully used as long as these tumors are of a more or less localized character, the practical significance of histologic grading rests upon its proper clinical interpretation into terms of prognosis and type of therapy best suited for the individual case, as indicated from the histologic malignancy grade.

II. *Malignancy grade and selection of type of treatment.*—Clinical experiences point to the fact that immature and highly anaplastic cancers are more successfully treated with X-rays and radium than by surgery, whilst mature and highly differentiated tumors with a low degree of anaplasia respond better to surgical treatment. The histologic grading of malignancy represents, therefore, the basis on which the decision as to the type of treatment best suited can be made by the clinician.

It is a rather widely accepted dogma among cancer therapists that the marked proliferative activity observed in the highly malignant tumors is the main cause for their good response to irradiation, whilst the small number of mitoses usually seen in highly differentiated and therefore less malignant cancers makes them less susceptible or even refractory to X-rays and radium. It is not denied that cells in the state of mitosis are radiosensitive, but recent experiments of Mottram[9] and Fischer[10] indicate that there are apparently active additional factors which influence radiosensitivity. Fischer asserts, from his observations on tissue cultures, irradiated with mesothorium, that the quantitative effect of irradiation on slowly and rapidly growing cultures is proportionally the same. Mottram, on the other hand, emphasizes the importance of the environmental factors on the "radiosensitivity" of the tumor.

But beside these more or less cellular aspects of irradiation effects, two factors exist in the vital qualities of highly malignant tumors which make them more suited for irradiation therapy. The one factor is the more diffuse infiltrative local growth of cancer cells of highly malignant tumors which makes their surgical eradication difficult and is the cause of subsequent local and distant recurrences after this procedure. The homogeneous penetration of the involved area by X-rays or radium rays guarantees the effect of the therapeutic agent on all tumor cells present in the irradiated region. The second factor is the great tendency of immature tumors to produce metastases at a time when the primary neoplasm is still relatively small. Also, here, irradiation of the regions of the lymphatic drainage will more effectively attack, for purely physical reasons, the scattered malignant cells than surgery can hope to accomplish.

While therefore an improvement in the curative results in highly malignant tumors by the use of rays can be expected and is observed, it seems to be very unlikely that irradiation treatment should transform in a paradoxical manner these otherwise highly dangerous tumors into new growths offering the best curative prospects. Carcinomas of the uterine cervix do not represent an exception, as the generally held conception that these

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cancers rarely extend beyond the upper rim of the pelvis, and remain therefore more or less local allowing the application of a sufficient amount of irradiation, is not correct according to the investigations of Maljeff[4] and Ford,[11] and, quite recently, of Warren.[8] The latter author, who studied the metastatic spread of seventy-four cases of cervical cancer at autopsy and compared his findings with the grades of malignancy, found the following correlations:

Visceral metastases were present in 35 per cent. of the cases; they were distributed on the different grades as follows:

	Cases	Per Cent. Not Extending Beyond the Upper Pelvic Rim
Grade I	21	86
Grade II	34	44
Grade III	11	0
Adeno-acanthoma	4	0
Adeno-carcinoma	4	0

Considering these findings and the more or less local effects of irradiation therapy, the remarkable curative results of Healy,[2] who obtained ten times as many cures in "advanced" highly malignant cervical cancers (group III) as in "advanced" low malignant cancers (group I), that is, 42 per cent. in group III against 4 per cent. in group I, require certainly an explanation which cannot be based on differences in radiosensitivity of these groups. Variations in radiosensitivity may change in degree, but not in substance, the rule being that the higher the grade of malignancy, the worse the prognosis.

While the grade of histologic malignancy is helpful in the selection of the most suited type of treatment, it should not influence the extent and the intensity of the treatment. Any cancer, regardless of its grade, must be attacked with all available means and to the limit of the therapeutic possibilities.

III. *Malignancy grade and prognosis.*—The grading of cancers is at present always a group grading and not a grading of the individual case. The grade places the tumor in a group of tumors which have according to empirical observation a certain percentage of cures. As cures, with our present therapeutic means, mainly depend on the absence of metastases, the histologic grade of malignancy expresses also the tendency of the tumor to form metastases. A high degree of histologic malignancy represents, therefore, an indication for a less favorable prognosis than that present in a case with a low-grade malignancy, if all other factors are equal. A case with a high-grade malignancy should, therefore, be especially carefully examined for distant metastases and should be frequently watched after operation or irradiation for the manifestation of such formations using all available methods for early detection (X-ray pictures, sedimentation tests, pH determinations of the blood, *etc.*).

It should be, moreover, kept in mind by the clinician that the histologic grade is only one of several factors which determine the prognosis of a

cancer patient, and that a relatively reliable prognostication can be obtained only if the significance of these various factors is properly gauged.

If the effect of a correct or incorrect treatment on the outcome of the disease be disregarded, the extent and the location of the cancer are the most important factors which determine the ultimate result. The clinical grouping of cancers as done by Schmitz and others have shown in a clear and convincing way the prognostic value of the first-mentioned factor. The combined effect and prognostic interrelation of extent and grade have been demonstrated by Hueper through an evaluation of 117 cancers of the breast and uterine cervix in regard to extent and malignancy index.

Malignancy Index	Clinical Groups		
	I	II	III
32–44	100	100	86
45–56	100	70	53
57–68	60	45	27

3 years' good end-results in percentages

An indirect relation exists between the prognostic significance of the malignancy grade and the extent. The prognostic value of the grade decreases with the increase in the extent of the tumor. The determination of the grade is, therefore, without any practical value as far as prognosis is concerned in generalized cancers. This statement in connection with several others made above illuminates also the scientific value of investigations in which it was attempted to determine the merits of the methods of grading by grading sections of breast cancers taken at random without consideration of the source of the section, extent of disease, *etc.*, and expressing the grade in terms of life expectancy of the individual case (one, two and three years). Such attempts are, indeed, pure guess-work and doomed to failure.

The second important clinical factor which has to be considered in any prognostication is the location of the tumor. The well-known variations in the curative results obtained in cancer of the cervix uteri and corpus uteri as well as of the cancers located at the base of the urinary bladder and at the dome of this organ may illustrate the importance of this factor.

There exist many other factors which have a bearing upon the prognosis, which are, however, less well known in their mechanism and effect and can therefore less definitely be evaluated (gross type of tumor, heredity, etiology, general status of patient, *etc.*). I may mention in this connection only one more factor which was recently discussed and investigated by McDonald and associates—it is the pH of the blood. McDonald found that untreated cancers with an alkaline pH of the blood show a shorter life expectancy than those with a normal or relatively acid pH. In subsequent correlative studies of Hueper it was demonstrated that cancers with an alkaline pH of the patient's blood are predominantly of an immature type, a factor which may account for the differences in longevity observed by McDonald. These observations bear out, also, the statement of Flothow[1] that the degree of differentiation of a tumor is a function of its environment.

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CONCLUSIONS

(1) Sections removed for grading must be taken from the peripheral zone of the tumor, must be properly prepared and stained and evaluated by a pathologist familiar with the method of grading.

(2) Grading is helpful in the selection of the type of treatment best suited in the individual case.

(3) The malignancy grade must never interfere with the extent or intensity of treatment.

(4) The malignancy grade indicates the proliferative and metastatic tendencies of a cancer.

(5) A reliable prognostication of a cancer must include at least three factors: The malignancy grade, the extent, and the location of the tumor.

BIBLIOGRAPHY

[1] Flothow: Surg., Gynec. and Obstet., vol. xlvi, p. 789, 1928.

[2] Healy: Am. Jour. Obstet. and Gynec., vol. xvi, p. 15, 1928.

[3] Hueper: Arch. f. klin. Chir., vol. clix, p. 200, 1930; Am. Jour. Cancer, to be published.

[4] Maljeff: Arch. f. Gynaek., vol. cxxxi, p. 339, 1927.

[5] Woodward, Schoonover, Fry, Torrance and McDonald: Jour. Clin. and Lab. Med., vol. xvi, p. 704, 1931.

[6] Wood: Jour. Am. Med. Assoc., vol., xcv, p. 1141, 1930.

[7] Reimann: Arch. Pathol., vol. viii, p. 803, 1929.

[8] Warren: Am. Assoc. Pathol. and Bacteriol., Cleveland, 1931.

[9] Mottram: Acta Radiol. Scand., vol. xii, p. 1, 1931.

[10] Fischer: Strahlenther, vol. xl, p. 54, 1931.

[11] Ford: Minnesota Med., vol. xiii, p. 489, 1930.

A BACTERIOLOGICAL STUDY OF CHRONIC ULCERATION IN RELATION TO CARCINOMA *

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THIS study involves a clinical, bacteriological and serological correlation of forty-one identical strains of streptococci isolated by anaërobic tissue cultures from twenty-four resected ulcers of the stomach, five of which were carcinoma, two were from ulcerative colitis with large adenomatoid hyperplastic polyps, two were from carcinoma of the rectum, eight from the cervix, and three from carcinomata of the breast.

All these organisms are proved identical by agglutination, cross agglutination and agglutinin absorption, and in turn they are proved identical morphologically and culturally with the streptococcus lacticus which may be consistently isolated from cows' milk. Because of these facts a correlation might be made of the following disease groups: gastric and duodenal ulcer, ulcerative colitis, infectious granuloma and polyposis of the intestine, chronic cervicitis and Hodgkin's disease and carcinomata.

Microbic dissociation is the determining and all-important factor in this correlation. Without going into a detailed description of the dissociation of this streptococcus, may it be said that on initial culture, bits of tissue seeded in the depths of $\frac{1}{2}$ per cent. semi-solid hormone agar, it appears as a fine filament and small coccus. After repeated transplants and gaining the ability to grow aërobically, it varies morphologically from a diphtheroid-like rod, solid-staining rod and beaded rod to a short and long chained lanceolate coccus. These morphological changes of the individual organism occur as the colony type changes from S—R.

The life cycle may be said to parallel, therefore, that of the mycobacterium group which Kahn has recently demonstrated, and has morphological similarities to the *mycobacterium Phlei* and the *mycobacterium graminis* found in plant dust and cultivated soil and the *mycobacterium stercussis* found in dejecta of cows. The market butter *mycobacterium rubropertinctum* and *Friburgense* may have had the same origin. The infectious granuloma type of disease of the intestinal tract of cows is due to the same type of organism, the *mycobacterium para-tuberculosis.*

This supposition is strongly substantiated when one observes the many

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TABLE

Cultural and Serological Relationship of All Strains

Culture	Source	Haemolysis of blood	Agglutination with sera 2 and 66 titre 2 1-12800 66 1-6400	Agglutination after absorption with sera 2 and 66	Fermentation reaction esculin bile	Sodium thiosulphate media—degree of blackening by sulphur production	Acidity figure change of 1% glucose broth from 7.4 to	Mannite fermentation	Heat resistance growth on 1% lactose agar after heating at 63° for 45'	Lactose fermentation in 24 hours
2	Gastric ulcer	A	1-12800	0	+	++	4.4	+	+	+
9	Dog ulcer	A	1-6400	0	+	++	4.4	+	+	+
19	Gastric ulcer	A'	1-12800	0	+	+	4.5	+	+	+
20	Gastric ulcer	A'	1-12800	0	+	+	4.6	+	+	+
23	Gastric ulcer	A	1-12800	0	+	++	4.4	+	+	+
45	Gastric cancer	A'	1-12800	0	+	+	4.3	+	+	+
46	Duodenal ulcer	A	1-12800	0	+	+	4.3	+	+	+
47	Gastric ulcer	A	1-12800	0	−	+	4.5	−	+	−
53	Gastric ulcer	A'	1-12800	0	+	+	4.6	−	+	+
55	Gastrojejunal ulcer	A	1-12800	0	+	+	4.5	+	+	+
56	Gastrojejunal ulcer	A	1-12800	0	+	++	4.6	+	+	+
58	Gastric ulcer	A'	1-6400	0	+	++	4.3	+	+	+
59	Gastric cancer	A'	1-12800	0	+	+	4.6	+	−	+
60	Gastric cancer	A'	1-12800	Trace 1-100	+	++	4.6	+	−	+
61	Gastric ulcer	A'	1-6400	0	+	++++	4.3	+	+	+
62	Gastric ulcer	A'	1-12800	0	+	+++	4.4	+	+	+
63	Gastric ulcer	A'	1-6400	0						
64	Duodenal ulcer	A'	1-6400	0	+	+++	4.4	+	+	+
66	Gastric cancer	A'	1-6400	0	+	++	4.4	+	+	+
67	Duodenal ulcer	A'	1-6400	Trace 1-100		+++				

No.	Source	Type	Titre	Trace						
68	Gastric ulcer	A'	1–6400	Trace 1–100	+	++	4.4	–	+	+
74	Gastric ulcer	A	1–3200	0	–	+	4.4	–	–	–
79	Gastric cancer	A	1–3200	0	–	+	4.3	+	+	+
79B	Blood-stream gastric cancer	B	1–3200	Trace 1–100	+	+	4.4	+	+	+
83S	Gastric ulcer	A	1–3200	Trace 1–100	+	+	4.5	–	–	–
83R	Gastric ulcer	A	1–3200	Trace 1–100	+	+++	4.4	+	+	+
69	Breast cancer	A	1–3200	0	+	++	4.5	+	+	+
70	Breast cancer	A	1–3200	0	+	++	4.2	+	+	+
73	Breast cancer	A	1–3200	0	+	++	4.6	+	+	+
81	Rectal cancer	B	1–6400	0	+	+++	4.8	+	+	+
82	Rectal cancer	B	1–3200	0	+	+++	4.6	–	–	+
84	Ulcerative colitis	A'	1–6400	Trace 1–100	+	++	4.4	+	+	+
85	Ulcerative colitis	A'	1–6400	0	+	+++	4.4	+	+	+
225	Cervix	A'	1–3200	Trace 1–100	–	++	4.6	–	+	–
226	Cervix	A'	1–3200	0	+	+++	4.2	+	+	+
253	Tissue uterus	A'	1–3200	0	+	+	4.7	+	+	+
255	Tissue uterus	A'	1–6400	0	+	+	4.7	+	+	+
263	Tissue uterus	A'	1–3200	Trace 1–100	–	++	4.7	–	–	–
266	Uterine swab	A'	1–6400	0	–	++	4.6	+	+	+
273	Cervix	A'	1–3200	0	+	+++	4.6	+	+	+
274	Uterus	A'	1–3200	0	+	+++	4.3	+	+	+
90	Cows' milk	A'			+	+++	4.4	+	+	+

NOTE.—(1) Strains 63 and 67 lost before cultural work completed; (2) titre figure is end-point of agglutination; (3) cultures 2 through 58—agglutination against serum 2; cultures 59 through 274—agglutination against serum 66; (4) culture 90 too recent to homogenize for agglutination and absorption.

morphological stages in its life cycle, which may be brought out *in vitro* by environmental changes.

Gastric and Duodenal Ulcer.—Whether one believes or not that the isolation of an identical organism from twenty-four resected ulcers proves it to be the etiological factor, the fact of its being there constantly and not a casual finding cannot be denied. And it is the constant finding of every bacteriological investigation of this disease.

The only other method of experimental approach warranting consideration, that of surgical duodenal drainage, has proved much less constant. Only one out of seven identical surgical duodenal drainage operations, performed by senior students, resulted in the production of an ulcer. This would suggest, then, another factor besides the loss of alkaline duodenal contents. Other investigators have had a higher percentage of positive results.

The organism has been shown to produce ulcers in the dogs' skin when injected intradermally, has been demonstrated in immediately fixed levaditi-stained sections of ulcers in great numbers, and its inability to grow in media containing bile of extremely low dilutions assured.

Patients suffering from gastric ulcer have this organism's specific agglutinins in their blood serum in 100 per cent. of cases tested, while those suffering from any other type of streptococcus infection fail to agglutinate or only in low titre.

In one case the organism isolated by tissue culture from a carcinomatous gland of the stomach was proved identical serologically with the organism isolated from the blood-stream, when bacteræmia occurred on the eighth postoperative day.

Ulcerative Colitis and Carcinoma of the Rectum.—The same streptococcus has been isolated from two positive carcinomata of the upper rectum and from two extreme cases of ulcerative colitis with carcinomatous-appearing constrictions and diffuse adenomatoid hyperplastic polyps of the upper rectum. On biopsy, however, a positive diagnosis of carcinomata could not be made. The bits of tissue in each case were cauterized and placed in formalin for a short while to prevent contamination with the entire intestinal flora. When contaminants were present, they were easily obviated by cracking the tube and recovering the growth in the depths of the semi-solid media.

It is well established that the Beta type of streptococcus rarely occurs in the colonic flora and the Alpha type is relatively infrequent when there is no evidence of disease. In a large series of patients suffering from complete anacidity of the stomach, Torrey rarely found these types in the stool specimen. The occasional surviving salivary type found in the intestinal flora is readily differentiated by its cultural and morphological characteristics.

The bowel streptococcus described by Dible is culturally identical with this organism in all of its major characteristics except that of hæmolysis, which he believes does not occur. Hæmolysis is indicative of increased virulence and when isolated from active pathological processes they are hæmolytic. Their hæmolytic activity is gradually lost on artificial cultivation.

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The diplococcus isolated by Bargen from ulcerative colitis is morphologically and culturally identical with this type. Ayres and Johnson found their enterococci indistinguishable in their major characteristics from typical lactic-acid cocci of milk, and they, with Dible, conclude that they are either closely related or identical.

The infective granuloma, chronic tumor-like productive inflammation of the gastro-intestinal tract, so ably reviewed by Mock, are identical pathologically with the adenomatoid hyperplastic polyps of advanced ulcerative colitis.

Fitzgibbon and Rankin, in their review of polyposis of the colon, found that carcinomata of the large bowel could be traced back through unbroken lines to polyps. They believe that the genealogical evidence for these growths, and that to be found in the literature for other similar carcinomata, argue persuasively for the extremely plausible contention that the histogenesis of carcinoma of the colon is mediated through pre-cancerous polyp formations and not otherwise.

Verse has described the earliest carcinomata of the stomach found in routine post-mortem examinations, and in each case the origin was on an acute inflammatory base with polymorphonuclear infiltration. This evidence would then seem a much better criteria of carcinomatous origin than the pathological study of full-grown carcinoma.

Cooke has reviewed the literature of carcinoid tumors of the small intestine and found reports of twenty-one malignant and eighty-three benign such tumors, the greatest proportion occurring in the distal ileum.

Hodgkin's Disease.—Singer has lately reported a case of primary isolated lymphogranulomatosis of the stomach and was able to find only six other reports in the literature. David later reported another, which, although microscopically lymphogranulomatosis, he called a pseudo-carcinoma of the stomach. The patient died later following development of a rectal mass which was presumably Hodgkin's infiltration.

To these eight cases may be added two from the Second Surgical Service of Bellevue Hospital. One, a man aged forty-five years, was operated upon by Doctor Hartwell in 1920 for gastric ulcer. The ulcer was locally excised. Dr. James Ewing pronounced it histologically typical to Hodgkin's disease but felt a malignancy could not be ruled out. The patient died twenty-two months following operation from a progressive cachexia and inability to eat.

The other case, culture 85 in this series, presented a mass in the upper rectum and sigmoid felt at operation to be a carcinoma. Proctoscopy had shown a diffuse ulcerating mucosa and a biopsy specimen for culture and diagnosis was taken. Dr. Douglas Symmers said it was histologically Hodgkin's disease.

The best experimental work on Hodgkin's disease may be correlative and not conflicting. Bunting and Yates cultured a pleomorphic diphtheroid from Hodgkin's gland and claimed to be able to produce a similar disease in monkeys by its injection. Torrey, in 1918, found anaërobic diphtheroids frequently in Hodgkin's gland, which he termed the *bacillus lymphophilus,* but also isolated it from other types of abnormal glands, and, therefore, did not feel it was the etiological factor.

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L'Esperance inoculated chickens intravenously with emulsions of Hodgkin's nodes and they all developed typical or atypical tuberculosis, and tissue smears showed acid-fast and non-acid-fast granules and rods. Growth of bacteria from these lesions showed the staining and cultural characteristics of an Avian tubercle bacillus.

Chretien, Germain, and Raymond showed that Avian tuberculosis manifests itself in a variety of forms but attacks principally the spleen and lymphoid apparatus, with a characteristic immunity of lungs. They classify two forms: the nodular and neoplastic types—the first granulomatous in character, the second showing an active proliferation of large polyhedral cells exhibiting a tendency to infiltrate surrounding structures. It exhibits many of the features of a neoplasm. What could more logically be the source of infection in birds than the dejecta of cows and horses and the fertilized soil? It is highly probable that this organism is one and the same in different stages in its life cycle, and isolated as a granule, rod, bacillus or coccus, due to the environment in which it has been growing.

Cervix Uteri.—Eight cultures, kindly given to us by Dr. William Park, were isolated from the cervix uteri during post-mortem infection and puerperal sepsis. The intestinal streptococcus is by far the most frequent infecting organism of the female genital organs, especially chronic endocervicitis. It may be considered a normal inhabitant of the vaginal vault and has been found in 70 per cent. of a series of cases examined. (Dible.)

Maryan has recently completed a study of tissue cultures from chronic cervicitis and was able to grow a streptococcus which biologically and morphologically was identical for forty-one of fifty-one cases of trachelectomy specimens. This organism confirmed morphologically and culturally to the enterococcus type of Dible.

A most exhaustive study of the pathological changes noted in 850 cervical specimens has been made by Bailey. He has outlined most carefully the individual developments occurring in acute cervicitis and chronic endocervicitis. He has followed the notable changes in the squamous and columnar epithelium, due to continued irritation of the infecting agent by serial sections, and has determined the resultant effect upon the new highly sensitive basal cells that cannot withstand the effects of constant irritation in any amount without proliferative activity and carcinomatous degeneration.

Carcinoma of the Female Mammary Gland.—The identical streptococcus has been isolated from three carcinomata of the female mammary glands in the same manner. Controls of normal breast tissue away from the carcinomatous area gave sterile cultures, as did two fibromata removed from the breast.

The pleomorphism of this streptococcus type is best illustrated by culture 75 isolated from one of the above three cases. The growth did not appear from the tissue until the eighth day. On staining it showed fine filaments and many granules. On continued culture, gradually gaining the ability to grow

aërobically, it became a diphtheroid bacillus, a solid rod, a beaded rod and finally remained stable as a short, chained streptococcus.

Nuzum isolatd a micrococcus from thirty-eight of forty-one human breast carcinomata and from more than 100 mice bearing transplantable Crocker fund carcinoma No. 11. By injecting these organisms into and under the skin of mice he obtained warts, epithelial horns and spreading cutaneous ulcers with localized epithelial hyperplasia.

Warren and Pearce repeated Nuzum's work both with his organism and with diphtheroid and micrococci cultures which they had isolated from human breast carcinomata. Inoculation into the breast of rabbits caused scarring and swelling of connective-tissue cells which resembled epithelioid cells in a tubercle. Hyperplasia of the duct epithelium and mitoses were noted. They also produced the chronic ulceration of the skin which Nuzum had done. They felt that these organisms did not play a primary rôle in the etiology of cancer though an indirect rôle, they felt, was possible.

It is doubtful whether such experimental attempts are a fair test of this theory. An animal's life is too short to permit in any way the reproduction of the conditions as they occur in man.

A vaccine and a filtrate of this organism were made for a skin sensitivity test. Three patients suffering from inoperable carcinoma of the breast showed a definite large wheal lasting twenty-four hours to an intradermal inoculation of the vaccine. Six patients suffering from breast abscesses (all nursing mothers) showed no reaction. The pyogenic breast abscesses, therefore, probably have no influence on breast carcinomata.

Lee states that the rapidly growing carcinoma of the breast in the young simulates an infectious process. He has reported thirty-eight cases which he classifies as inflammatory carcinoma.

Discussion.—In a previous article the metabolism of this streptococcus was cited in comparison with the metabolism of the carcinoma cell as brought out by Otto Warburg. Both are anaërobes and both by glycolysis produce lactic acid. He has shown that lactic acid is necessary for the growth and spread of carcinoma cells.

Hammett concludes, "that the —SH, incompletely oxidized—SH groups, comprise the chemical elements of the naturally occurring chemical equilibrium through which growth by increase in cell number is regulated. He has shown that at a pH 5.5, where the sulphur is in the reduced state, stimulation occurs, and at a pH 7.2, where it is in the suboxidized state, retardation takes place, and that between a pH 6 and 7, where equilibrium exists between the reduced and suboxidized sulphur, no consistent direction of response is registered.

As a result of this work, Reimann prepared an —SH compound (thiocreasol) and both in experimental wounds and in human stubborn ulcers found that it stimulated mitosis and wound healing.

Cysteine and glutothione, compounds active in the oxidation and reduction processes of the body and present both in the circulating blood and other body tissues, are characterized by the —SH or sulph-hydral group.

With the foregoing facts in mind, an understanding of microbic dissociation and a glance at the table showing lactic-acid and sulphur production by the organism which coupled with its mannite fermentation and tremendous heat resistance differentiates it from all other streptococci and proves its identical relationship with the *streptococcus lacticus* of cows' milk, the following hypothesis can be formulated:

That the chronic ulcerative lesion of years' duration which has finally started to show proliferative activity and uncontrolled cell division may be due to the following factors:

(1) Continuous repair; (2) poor blood supply and lymph return; (3) the presence of the streptococcus described, which is characterized by (a) remarkable vitality (heat resistance above that of pasteurization); (b) lactic-acid production reducing pH of tissue to 4.2 to 4.8, which keeps sulphur in stimulatory phase; (c) hydrogen-sulphide production; (d) anaërobians.

As a result of these four major characteristics, there is brought about a hydrogen-ion concentration and an oxidation and reduction potential in which the sulph-hydral group, present in all tissues in the form of cysteine and glutothione, is stimulatory to cell division.

BIBLIOGRAPHY

[1] Mann, F. C., and Williamson, C. S.: The Experimental Production of Gastric Ulcer. ANNALS OF SURGERY, vol. lxxvii, p. 409, 1923.

[2] Torrey, J. C.: Bacteria Associated with Abnormal Lymph Glands. The Journal of Medical Research, vol. xxxiv, p. 65, March, 1916.

[3] Dible, J. H.: A System of Bacteriology. Medical Research Council, vol. ii, London, 1929.

[4] Ayers and Johnson: Quoted by Dible.

[5] Mock, H. E.: Infective Granuloma. Surg., Gynec., and Obstet., vol. lii, p. 672; March, 1931.

[6] Fitzgibbon, G. and Rankin, F. W.: Polyps of the Large Intestine. Surg., Gynec., and Obstet., vol. lii, p. 1136, June 1931.

[7] Versé: Quoted by Ewing. Neoplastic Diseases. Ewing. W. B. Saunders Co., publishers.

[8] Cooke, H. H.: Carcinoid Tumors of the Small Intestine. Arch. of Surg., vol. xxii, April, 1931.

[9] Singer, H. A.: Primary Isolated Lympho-granulomatosis of the Stomach. Arch. of Surg., vol. xxii, April, 1931.

[10] David, V. C.: Pseudo-carcinoma of the Stomach. ANNALS OF SURGERY, vol. lxxxvii, p. 55, April, 1931.

[11] Bunting, and Yates: Journ. A. M. A., vol. lxii, p. 516, February, 1914.

[12] L'Esperance, Elise S.: Experimental Inoculations of Chickens with Hodgkin's Nodes. Journ. of Immunology, vol. xvi, p. 37, January, 1929.

[13] Chrétien, Germain, and Raymond: Revue de la Tuberculose, vol. iv, p. 25, February, 1923.

[14] Maryan, H. O.: Bacteriology of Deep Tissue Cultures from Chronic Cervicitis. Pro. Soc. Exp. Bi. and Med., vol. xxviii, p. 733, April, 1931.

[15] Bailey, K. V.: An Inquiry into the Basic Cause and Nature of Cervical Cancer. Surg. Gynec., and Obstet., vol. l, p. 513, March, 1930.

[16] Nuzum, J. W.: Surg., Gynec., and Obstet., vol. xxxiii, p. 167, 1921; and vol. xl, p. 343, 1925.

[17] Warren, S. L., and Pearce, H. E.: The Repeated Inoculations of Animals with So-called Cancer Organisms. Amer. Journ. of Med. Sci., vol. clxxi, p. 820, June, 1926.

[18] Lee, B. J.: Carcinoma of the Breast in the Young. Arch. of Surg., vol. xxiii, p. 85, July, 1931.

[19] Warburg: Uber den Stoffwechsel der Tumoren. Arbeiten ans dem Kaiser Wilhelm. Institut für Biologie, J. Springen, vol. xxi, pp. 8–263, Berlin, 1926.

[20] Hammett, F. S.: The Natural Chemical Equilibrium Regulative of Growth by Increase in Cell Number. Protoplasma, vol. xi, No. 3, pp. 382–410, 1930.

[21] Reimann, S. P.: Use and Reasons for the Use of Thiocreasol to Stimulate Wound Healing. Journ. of the Amer. Med. Assoc., vol. xciv, p. 1369, May, 1930.

[22] Saunders, E. Watts: The Serologic and Etiologic Specificity of the Alpha Strep-tococcus of Gastric Ulcer. Arch. of Internal Med., vol. xlv, p. 347, March, 1930.

[23] Saunders, E. Watts: A Bacteriological and Serological Study of Gastric Ulcer. ANNALS OF SURGERY, vol. xci, p. 222, August, 1930.

[24] Saunders, E. Watts: Is There a Specific Bacterial Irritant to Four Sites of Carcinoma? Amer. Journ. of Cancer, vol. xv, No. 4, p. 2745, October, 1931.

A STUDY OF THE RESULTS OF OPERATIONS FOR THE CURE OF CANCER OF THE BREAST

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SINCE 1894, when Doctor Halsted first reported "Results of Operations for the Cure of Cancer of the Breast," performed on fifty consecutive patients at the Johns Hopkins Hospital, embracing a period from 1889, the year when the hospital was opened, there were published by him from time to time further studies of these, and additional cases which were treated at the hospital in the succeeding years. The first report of these studies was made in 1894, to be followed by others in 1898, 1907 and 1912. It therefore seemed fitting to us that the results of a further study, which includes not only later observations of the cases previously reported by Doctor Halsted, but as well those which have been treated at the Johns Hopkins Hospital since 1912, should be reported. This present study embraces a period of forty-two years, from 1889 to 1931, and includes a series of 950 consecutive cases. As would be expected and as was predicted by Doctor Halsted in the earlier reports, the estimation of the results of treatment from a statistical point of view must be constantly revised, at least until a sufficient number of years have elapsed after operation for a numerically representative group of patients to have died of carcinoma or other diseases, or to have completed their normal life expectancy—in other words, until there has accumulated a series of patients of sufficient number who have died over a period of years sufficiently long after their operation to have been afforded the opportunity of completing their normal span of life. It is to be expected that even so there will be marked and unavoidable fluctuations in the estimation of the results because of the unknown factors involved in the disease, and the individual variations of the patients.

Of the 950 patients considered in the study, 420 (44.2 per cent.) are known to have died, and accurate data pertaining to their post-operative length of life as well as other points of interest could be obtained. It would therefore seem that the period of years of observation, namely, forty-two, together with the size of this entire group of 950, of which the known dead comprise 420 (almost 50 per cent.), would supply a sufficient length of time and number of patients from which at least fairly general conclusions may be drawn. Those patients who have been lost track of should be considered dead, but of course it is always possible that some of them, probably only a small number, may be found to be alive. In the present series this group numbered 209 (22 per cent.). Ninety-seven patients (10 per cent.) are alive

and well, and sixty-five (67 per cent.) of these have lived more than five years. It is again probable that over a period of forty-two years patients may succumb to diseases other than carcinoma. As will be pointed out later under the cause of death, a large percentage of patients apparently *died with, if not of, carcinoma.*

It is evident that the angles of approach from which our series may be studied are many. It is equally apparent that a relation of statistics would be uninteresting and prohibitive reading. We have therefore felt that a discussion of the main points of interest under a few separate headings would tend to increase the readability and decrease the confusion which must accompany a profusion of tables and figures. However, it is also felt that the statistical results of this analysis of these 950 cases should be recorded in detail, so that in the future they might be available for further study or comparison. For this reason all the tables and graphs are shown with their detailed descriptions given in the legends.

Attention is directed to the fact that we are appreciative of the presence of an inescapable error in our statistics, and therefore realize that our conclusions are in all probability incorrect to some extent, because further data obtained in regard to the patients who remain alive, or of the relatively large group which have been lost track of for the present, may alter these figures considerably. This point may be illustrated by the fact that in the first fifty cases reported by Halsted in 1894 there were three (6 per cent.) local recurrences. The second report in 1898 showed 9 per cent. of local recurrences, and of this original fifty cases, from which three have been removed as not being carcinoma, leaving forty-seven, we can now, in 1931, trace fifteen local recurrences or an increase in percentage of local recurrences from 6 to 31.9 per cent. We feel, however, that the size of this entire group (950 cases), especially that of the known dead (420 cases), together with the length of the period of observation, forty-two years, insures a certain stability to the statistical averages, and while there may be some changes in the future, we feel that they will be inconsequential.

It is, of course, possible for surgical statistics to be improved by the selection for operation of only those cases which were favorable, and again, operations that have been performed on cases in which the disease was very extensive may have been classified as incomplete. In order to determine, however, the true worth of an operative procedure for the cure of carcinoma, not only the favorable but also the extensive or unfavorable cases should be included. It is, of course, realized that the converse is also true: namely, that the efficacy of an operation cannot be judged if an attempt is made to treat cases in which the limits of operability have already been exceeded previous to the operation. The fact that in this series of 950 cases, over a period of forty-two years, only seventy-two (7.6 per cent.) were untreated because the lesion was thought to be inoperable, eliminates any possibility of a selection of cases having been made. It is also to be noted that in the early days of the hospital before 1910 the disease was as a rule more extensive on admission and the limits of operability were considered wider than at present. It is, therefore,

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felt that this series of cases constitutes a test for the operative treatment of carcinoma of the breast as severe as is possible with our present clinical methods and that the results in the future should with the same surgical technic and enthusiasm be better than in the past. Not infrequently at private clinics it is possible for certain individual operators, who devote themselves to one special operation or group of selected cases, to obtain results which are better than those to be expected from the average competent surgeon. Again, in this series of 950 cases 750 were operated upon in the Johns Hopkins Hospital by thirty-eight operators, eight of whom had never performed the operation before. Of the thirty-eight, thirty-one were either serving as Residents or had just completed a residency, so that the results of this series represent what may be expected from the application of a radical and meticulous surgical procedure in the treatment of carcinoma of the breast by a varied group of surgeons whose enthusiasm more often caused them to attempt to effect a cure of a hopeless case rather than a selection of favorable ones. In order to prevent or remove an ulcerated area but with no idea of curing the patient an incomplete operation was performed in only twenty-one cases or 2.2 per cent. Again, surgical statistics may be very much improved by the pathologist on whom the surgeon relies if he classifies as carcinoma, tumors in which the histological appearance is suggestive of malignancy in certain areas or is made up of malignant-appearing cells. This entire group of 950 cases have been examined from a pathological standpoint most thoroughly by pathologists who were entirely disinterested, *i.c.*, by Doctors Welch, Bloodgood, MacCallum, and their assistants. Recently these specimens were re-examined by Doctor Bloodgood.

The keen interest manifested by Doctor Halsted in the subject of perfecting a radical operation for the cure of carcinoma of the breast stimulated the remaining and succeeding members of the upper and residential surgical staff to perform the most meticulous type of dissecting operation, and in spite of the fact that the majority of the patients treated were public-ward cases with breast tumors that were classified as large and in which the disease was far advanced, the results from the standpoint of post-operative longevity and local recurrence, so far as we can discover, are unequalled. A number of years hence these remote results should be even better, for the affected breast is now operated upon at a very much earlier stage of the disease, and while the tumor is small. In these cases the operation should be, if possible, even more radical than in the cases of the larger tumors, for the opportunity to cure them is even greater. These points are emphasized because of the present-day tendency to withdraw somewhat from the stand of radical excision in favor of a less radical operation supplemented by the very questionable effect of radiation.

In order to determine the efficacy of the surgical treatment of carcinoma of the breast there are many important factors and influences which must be taken into consideration, such as the age of the individual and the activity of the gland, the type of tumor, the extent of the disease, the duration and size

TABLE I.—*Frequency Distribution of Patients with Carcinoma of the Breast, by the Year of Incidence, Also a Classification of the Patients According to the Most Recent Reports*

Johns Hopkins Hospital (1889–1931)

Years of incidence	Total No. of cases	No. of pts. known dead	No. of pts. of whom track has been lost	No. pts. living and well	Doubtful carcinoma	No. pts. not treated	No. pts. having recurrence but not dead. Prim. oper. J.H.H.	No. pts. having recurrence. Prim. oper. elsewhere	No. pts. having an incomplete oper.	No. of cases where there has been no follow-up	Carcinoma in super-numerary breast
1889	6	3	3					3		3	
1890	14	5						6		6	
1891	11	8	1					1		1	
1892	21	12	1					3			
1893	21	12	2								
1894	10	7	2								
1895	24	19	2	1		1		1	1		
1896	22	16		1							
1897	23	17	1	1	1	1		2	1	1	
1898	30	19				4		2			
1899	27	22	1	4		1		3			
1900	21	14	2	1 1		2	1	6			
1901	20	11	2		1	2		6			
1902	22	16	3	1 1		4	1	1	2		
1903	25	17	2	4		8	1	1			
1904	27	15	2	4		1	1	2			
1905	27	13	3	5		4	2	2			
1906	20	9	3	5		2	2	2			
1907	29	17	4	3	1	4	1	3			
1908	23	12	4	3	1	1	1	2			
1909	23	12	6	1		1	1	2			
1910	23	18	1	1	1	3	1	2			
1911	27	16	5	3		3	1	3			
1912	22	12	4	1		3	1				
1913	14	6	4	1		2	1	3			
1914	28	13	4	1		1	1	5			
1915	23	7	8	2		4	1	2			
1916	21	8	3	3		4		4			
1917	25	7	3	5		5					
1918	19	4	7	2	1		1		1		
1919	20	9	5	3	1	6	1				
1920	26	9	9	1			1	7	1		
1921	29	4	8	5	1		4	1			
1922	16	2	13	5	1	2	4	1			
1923	22	5	16	2	1	2		1			
1924	29	3	15	5	1		3	1			1
1925	18	3	9	5			3	1			
1926	28	4	13	7		1		1	1		
1927	24	7	10	6		1		2	2		
1928	21	2	13		2		1	1			
1929	20	1	12	5			1	4	1	12	
1930	31	2	6	6			1			6	
1931	8			1		1					
Totals	**950**	**420**	**209**	**97**	**11**	**72**	**24**	**77**	**21**	**18**	**1**
Per cent.	**1.000**	**44.2**	**22.0**	**10.0**	**1.2**	**7.6**	**2.7**	**8.1**	**2.2**	**1.9**	**.1**

Year of incidence is equal to year of admission to hospital. Of ninety-seven patients living and well sixty-five or sixty-seven per cent. have lived more than five years.

of the tumor, the type of operation, *etc.* These influences will be discussed in the following order under separate headings.

Yearly and Age Incidence Together with Marital Status and Sex.—(Table I.) The frequency distribution of the cases according to the year of their admission into the Johns Hopkins Hospital is considered the yearly incidence and varies only inconsiderably from 1889 until 1931. In this series, carcinoma

TABLE II.—*Frequency Distribution of 950 Cases of Carcinoma of the Breast as to Marital Status. Johns Hopkins Hospital (1889–1931)*

Marital status	No. of patients, female	No. of patients, male	Per cent. of patients, female	Per cent. of patients, male	Total no. patients	Per cent. of patients
Married.............	821	9	86.4	.9	830	87.3
Single..............	118		12.4		118	12.4
Unknown...........	2		.1		2	.1
Totals..............	941	9	98.9	.9	950	99.8

830 cases or 87.3 per cent. married. 118 or 12.4 per cent. unmarried. 9 or 0.9 per cent. were males whereas 939 or 98.8 per cent. were females.

TABLE III.—*Frequency Distribution of 950 Cases of Carcinoma of the Breast as to Marital Status and Color. Johns Hopkins Hospital (1889–1931)*

Marital status	White	Black	Per cent. white	Per cent. black	White males	Black males	Total no. patients
Married...	604	217	63.6	22.8	6	3	830
Single.....	98	20	10.3	20.1			118
Unknown..	1	1	.1	.1			2
Per cent....	74.0	25.1			.6	.3	
Total no. patients.	703	238			6	3	950

604 or 63.6 per cent. were white and 217 or 22.8 per cent. were black; while of those unmarried 98 or 10.3 per cent. were white and 20 or 20.1 per cent. were black. Of the males all were married. 6 or 0.6 per cent. were white and 3 or 0.3 per cent. were black.

of the breast has not occurred previous to the age of twenty or later than seventy-eight, but increases in the second and third decades of life to reach its maximum in the fourth decade, while the incidence subsides in the late seventies. This tendency occurs in the married and unmarried alike and is shown graphically in the curves A and B. It seems to be well ingrained in the surgical literature that married women are more frequently affected with carcinoma of the breast than unmarried. In Tables II and III may be seen the frequency distribution of these 950 cases as to the marital status, which would seem to support the above contention. However, when the marital status is tabulated in conjunction with the age incidence it is then possible to compare this group of 950 cases with an unaffected group of women of

similar size in the United States distributed according to the 1920 Census, both in regard to marital status and age. In our series of 950 cases the age incidence and marital status were as shown in Table IV, while that of the
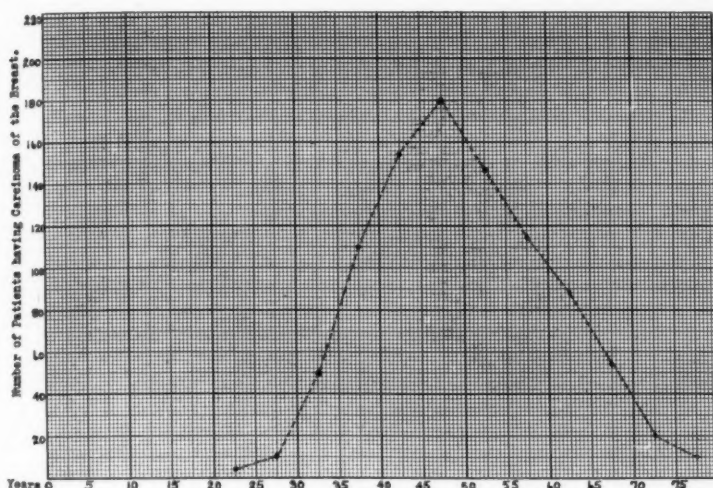
CHART A.—Age incidence of carcinoma of the breast. Figures given in the total column, Table IV. Number of cases, 950.

unaffected group of 950 women according to the Fourteenth Census of the United States, 1920, vol. ii, is given in Table V. For the sake of comparison of the two groups of 950 women affected and unaffected, the age groups of

TABLE IV.—*Frequency Distribution of 950 Cases of Carcinoma of the Breast as to Age Incidence and Marital Status. Johns Hopkins Hospital (1889–1931)*

Age in yrs.	Married	Single	Per cent. married	Per cent. single	Status unknown	Total	Per cent.
20–24.....	2	2	.2	.2		4	.4
25–29.....	8	2	.8	.2		10	1.1
30–34.....	38	11	4.0	1.2		49	5.2
35–39.....	95	15	10.0	1.6		110	11.6
40–44.....	132	22	13.9	2.3		154	16.2
45–49.....	163	16	17.2	1.7	1	180	18.9
50–54.....	128	18	13.5	1.9		146	15.4
55–59.....	96	18	10.1	1.9		114	12.0
60–64.....	80	8	8.4	.8		88	9.3
65–69.....	50	3	5.3	.3	1	54	5.6
70–74.....	19	1	2.0	.1		20	2.1
75 and over	8	2	.8	.2		10	1.1
Subtotals..	819	118	86.2	12.4	2	939	98.9
Males.....	9		.9			9	.9
Unknown..	2		.2			2	.2
Totals.....	830	118	87.3	12.4	2	950	100.0

Occurrence of carcinoma apparently increases through the second and third decades of life to reach a maximum in the fourth decade when the incidence subsides in the late seventies.

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Table IV were changed from five to ten years, as shown in Table VI.   Thus
Tables V and VI corresponded.   By taking the total number of women having
carcinoma of the breast in each age group and applying to it the percentages
given in the columns, married and single in Table V, the number of married
and single women that would be in each age group, if they were not affected
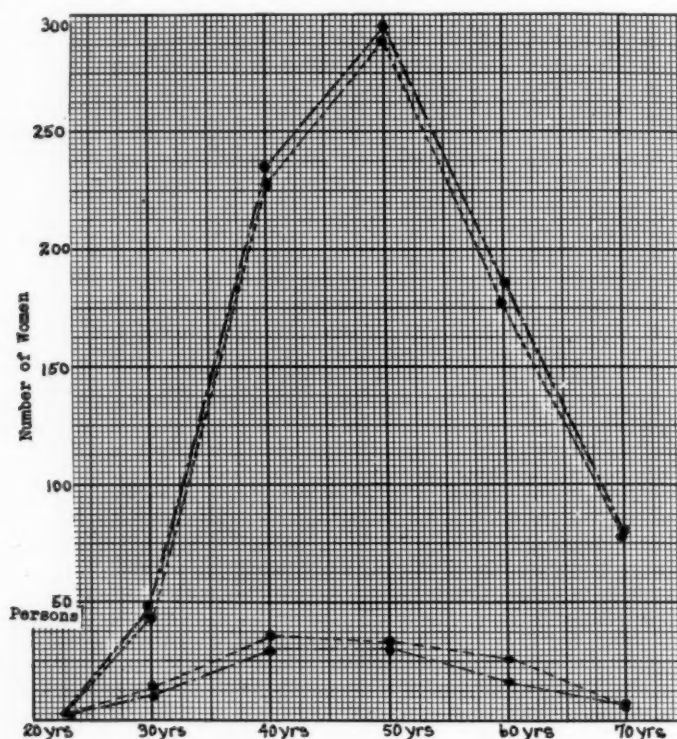
CHART B.—Diagram showing that carcinoma of the breast makes no selection as to the marital
status of women.   _ _ _ _ _   Age distribution of 819 married women having carcinoma of the
breast;   _._._._   Age distribution of 819 married women of the same age group (twenty to
seventy-five), according to the 1920 census, United States.   Age distribution of 118 single women
having carcinoma of breast,   _ _ _ _ _ _   Age distribution of 118 single women, of the same age
group (twenty to seventy-five), according to the 1920 census, United States _._._._._   Larger,
upper group records married women; smaller, lower group records single women.

by carcinoma of the breast, is determined.   These figures are given in Table
VII.   By comparing Tables VI and VII it is seen that the number in each age
group having carcinoma of the breast is almost identical with the group un-
affected by it.   Therefore, it is evident that the marital status played no part
in the occurrence of carcinoma of the breast in this series of patients.   This is
graphically shown in Chart B.

As stated above, it is also apparent from Table III that white women are
affected more frequently than colored; that this is only apparent is indicated
by a study of the proportion of white and colored women in the United States
as a whole, and Baltimore, Maryland, in particular.   In the United States as a
whole, there are 8.6 per cent. colored and 91.4 per cent. white women.   This
ratio is slightly higher in Baltimore, where there are 14.8 per cent. colored

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TABLE V.—*Marital Status and Age Distribution of All Classes of Females in the United States—1920**

Age in yrs.	Per cent. single	Per cent. married
All classes.............	50.7	49.3
Under 15.............	100.0	—
15 and over..........	27.3	72.5
15–19...............	87.0	12.9
20–24...............	45.6	54.3
25–34...............	19.3	80.6
35–44...............	11.4	88.6
45–54...............	9.6	90.3
55–64...............	8.4	91.5
65 and over..........	7.1	92.7
Age unknown........	28.0	57.7

* From Table V, Marital Condition of the Total Population by Sex and Age Periods for Principal Population Classes, for the United States; 1920, 1910, 1900. Pp. 394–395. Fourteenth Census of the United States, 1920, vol. ii, Population.

Percentage of single women in the United States decreases in each ten-year period from fifteen years of age on, while the percentage of married or widowed women increases in each ten-year period from fifteen years of age.

and 85.2 per cent. white women, or a ratio of 1:5.76 or practically 1:6. (From the United States Census, vol. ii, 1920.) In this series of 950 cases the ratio of colored to white women is 25 per cent. colored to 74 per cent.

TABLE VI.—*Frequency Distribution of 950 Cases of Carcinoma of the Breast as to Age Incidence and Marital Status (ten-year age groups)*

Johns Hopkins Hospital (1889–1931)

Age in yrs.	Married	Single	Per cent. married	Per cent. single	Status unknown	Total no. cases	Per cent.
20–24.....	2	2	.2	.2		4	.4
25–34.....	46	13	4.8	1.4		59	6.2
35–44.....	227	37	23.9	3.9		264	27.8
45–54.....	291	34	30.6	3.6	1	326	34.3
55–64.....	176	26	18.5	2.7		202	21.3
65 and over	77	6	8.1	.6	1	84	8.8
Subtotal...	819	118	86.1	12.4	2	939	98.8
Males.....	9		.9			9	.9
Unknown..	2		.2			2	.2
Totals.....	830	118	87.2	12.4	2	950	99.9

In working per cents. used 821 as total instead of 830 because 9 were males.

Ten-year age groups in this table obtained by transforming Table IV from five-year to ten-year groups in order to compare Table VI with Table V.

TABLE VII.—*A Hypothetical Case, Showing the Number of Married and Single Women That Should Be in Each Age Group: if the Ratio of Married to Single Is the Same As That for All Women in the United States*

Age in yrs.	Married women	Single women	Total
20–24	2	2	4
25–34	48	11	59
35–44	234	30	264
45–54	295	31	326
55–64	185	17	202
65 and over	78	6	84
Totals	842	97	939*

* Eleven cases were omitted because nine were males and the marital status of two was unknown.

By taking the total number of women having carcinoma of the breast in each age group and applying to it the per cents. given in the columns Married and Single in Table V, the number of married and single women that would be in each age group, if they were not affected by carcinoma of the breast, is determined. These figures are given in Table VII. By comparing Tables VI and VII, it is seen that the number in each age group having carcinoma of the breast is almost identical with the group unaffected by it. This is shown graphically in Chart B.

TABLE VIII.—*Distribution by Age Groups of Females of All Classes in the United States 1920**

Age in yrs.	Per cent. of females in each age group
Under 5	11.0
5–14	21.1
15–24	18.3
25–34	16.4
35–44	13.0
45–54	9.4
55–64	5.9
65 and over	4.7

* From Table II, Distribution by Broad Age Groups for Population Classes by Sex, for the United States, 1910 and 1920, p. 155. Fourteenth Census of the United States, 1920, vol. ii, Population.

Women of twenty-five years of age and older form 49.4 per cent. of all the females in the United States. Since in the carcinoma of the breast group there are 935 women, twenty-five years of age or more, this number represents the same 49.4 per cent. The size of a group of women, in which 935 are twenty-five years old or older is 1893, because 935:x::49.4:100. By applying the per cents. given in Table VIII for each age group to 1893, the number of women unaffected by carcinoma of the breast is determined for each age group as shown in Table IX.

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white, a ratio of 1:3, which is much higher than the normal distribution in the population as a whole. This would tend to suggest that the incidence of carcinoma of the breast is higher among colored than white women. The proportion of colored to white women admitted to the Johns Hopkins Hospital is 1:3 demonstrating that the incidence of carcinoma of the breast in the two races is about the same for this group of cases.

In an attempt to find out if carcinoma of the breast was selective for certain age groups a study was made of the age distribution of women in the United States as a whole and a comparison was made with the age distribution of this group of 950 cases. The fact that 49.4 per cent. of all the females in the United States are twenty-five years of age or older enabled us to compare
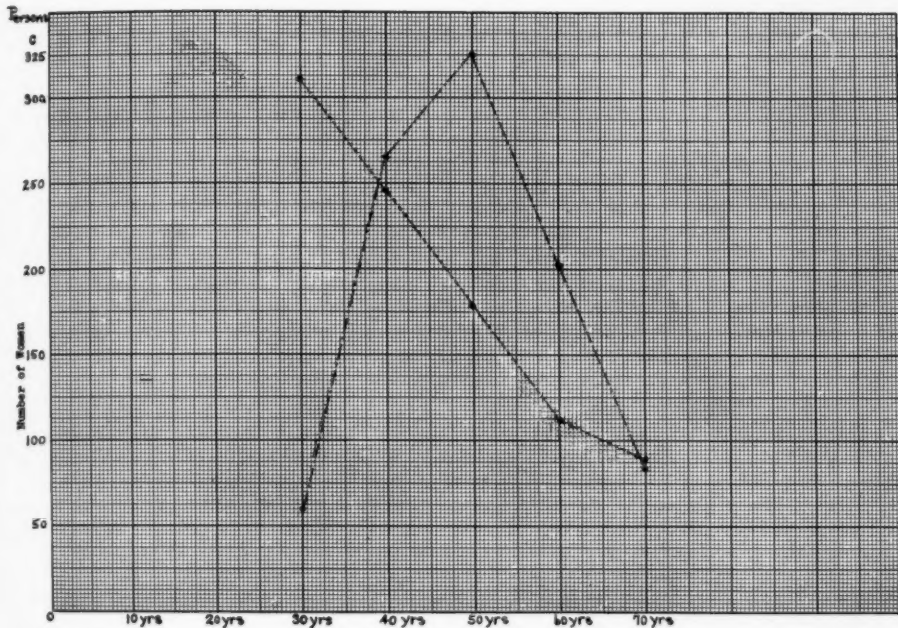
GRAPH C.—Diagram showing the selection carcinoma of the breast as to age. — — — — — Shows the age distribution of 935 women according to the age group percent from the 1920 census, United States. —.—.—.— Shows the age distribution of 935 women of the same age group who had carcinoma of the breast.

for each age group the women affected and unaffected with carcinoma of the breast. The method by which these comparisons were worked out mathematically may be observed in Tables VIII, IX and X, with their legends, and Graph C.

It will be noted that there is a constant diminution in the number of women in the United States in each age group from twenty-five years of age on. However, in the series affected with carcinoma of the breast there is an increase in the number of cases for each age group from twenty-five years of age on, reaching a maximum at about fifty, from which there is a gradual decrease. The greater number of cases of carcinoma of the breast in this series occurred between thirty-five and sixty-four.

Carcinoma in the male breast occurred only nine times in 950 cases, the details of which may be seen in Table XI.

TABLE IX.—*A Hypothetical Case Showing the Age Distribution of 935 Women over Twenty-five Years of Age, if Their Ages Were Distributed in Accordance with the Age Distribution of Women in the United States*

Age in yrs.	No. of women	Per cent. in each age group
25–34	310	16.4
35–44	246	13.0
45–54	178	9.4
55–64	112	5.9
65 and over	89	4.7
Totals.	935	49.4

If 935 women represent 49.4 per cent. of total, then the total is 1893 for 935:x::49.4:1.

The distribution according to the age incidence of women unaffected by carcinoma of the breast in a group of which the total is 1893 distributed according to the distribution of women in the United States. There is a constant diminution in the number of women in each age group from twenty-five years of age on.

Anatomical and Pathological Classification.—The situation of the tumor, as shown in Table XII, seemed to be about as frequent in the right as in the left breast and in only forty-five cases (4.7 per cent.) was the disease bilateral. Of these only fourteen (1.5 per cent.) had bilateral breast carcinoma on admission. In twenty-four cases it was possible to find the actual

TABLE X.—*Frequency Distribution of 935 Cases of Carcinoma of the Breast, over Twenty-five Years of Age, as to Age of Incidence. Johns Hopkins Hospital (1889–1931)*

Age in yrs.	No. of patients	Per cent.
25–34	59	6.3
35–44	264	28.2
45–54	326	34.9
55–64	202	21.6
65 and over	84	9.0
Totals.	935*	100.0

* Fifteen cases omitted, 9 males; 2 ages unknown; 4 were between the ages of twenty to twenty-four years. These last were omitted because the per cents. in the United States Census were given in ten-year age groups.

The actual distribution of the cases of carcinoma of the breast in this series of 950 cases according to their age incidence. There is an increase in the number of cases of carcinoma of the breast from twenty-five years of age on, reaching a maximum about fifty, from which there is a gradual diminution. The greater number of cases of carcinoma of the breast occur between thirty-five and sixty-four. This is not only apparent but actual, as shown by Graph C. Compare this table with Table IX.

time between the two admissions or operation. In fourteen cases, or 58 per cent., the remaining breast was involved by the end of the second year; in eighteen cases, or 75 per cent., by the end of the fifth year. (Table XIII.) However, in two cases the second breast did not become involved until eighteen

TABLE XI.—*Classification of Male Cases of Carcinoma of the Breast, as to Age, Marital Status and Color*

Johns Hopkins Hospital (1889–1931)

Yrs. of incidence	Age	Married	Single	White	Black	Patient's condition from most recent report
1892....	48	I		I		Incomplete operation
1893....	64	I		I		Dead
1898....	47	I		I		Dead
1900....	71	I		I		Recurrent, prim. oper. elsewhere
1903....	69	I			I	Dead
1917....	54	I			I	Dead
1922....	66	I		I		Lost track of patient
1923....	64	I		I		Not treated
1926....	63	I			I	Well
Totals...		9		6	3	

Average age incidence in male breast is greater than female. Two-thirds are over sixty years of age.

and twenty years after the first operation. It is, of course, possible that these may be instances of another growth *dc novo* instead of metastases from the primary one. The average length of life of the patients with bilateral involvement was 5.69 years, and therefore longer than for cases of carcinoma of

TABLE XII.—*Situation of Tumor in 950 Cases of Carcinoma of the Breast*

Johns Hopkins Hospital (1889–1931)

Situation of tumor	No. of cases	Per cent. of cases
Right breast.........	442	46.5
Left breast..........	463	48.7
Both breasts........	45	4.7
Totals..............	950	99.9

the breast as a whole because 42 per cent. of the former had already lived for two or more years before the second breast became involved and in 25 per cent. at least five years. This average life is computed from Table XIV.

The pathological classification of this group of 950 cases is interesting primarily because excepting eleven, or 1.2 per cent., doubtful cases and 123, or 12.9 per cent., unknown, as shown in Table XV, the remainder are unques-

TABLE XIII.—*Bilateral Cases of Carcinoma of the Breast; Showing the Time That Elapsed between the First and Second Admissions or Operations*

Time in yrs.	No. of cases
1	6
2	8
3	1
4	2
5	1
6	2
7	1
10	1
18	1
20	1
Bilateral at admission	14
Unknown	7
Total	45

In several incidences there was no second operation.

In 45 cases out of 950, or 4.7 per cent., the disease was bilateral. Fourteen or 1.5 per cent. had bilateral breast carcinoma on admission. In twenty-four cases it was possible to find the actual time between the two admissions or operations. In fourteen cases or 58 per cent. the second breast was involved by the end of the second year. In eighteen or 75 per cent. by the end of the fifth year. In two cases the second breast did not become involved until eighteen and twenty years after operation.

TABLE XIV.—*Length of Post-operative Life for the Cases of Carcinoma of the Breast Where There Was a Bilateral Involvement*

Post-oper. life in yrs.	No. of cases
1	6
2	6
3	4
4	3
5	3
6	4
7	—
8	2
9	1
10	1
11	1
12	—
13	1
—	—
19	1
20	2
Unknown	10
Total	45

The average length of life of the cases with bilateral involvement was 5.69 years, therefore greater than for the cases of carcinoma of the breast as a whole because 42 per cent. of these cases had already survived two years before the second breast was involved, and in 25 per cent. at least five years.

tionably cancer. In the remaining group, by far the greater number consisted of scirrhous carcinoma (51.2 per cent.) with medullary next in frequency (22.4 per cent.). Adeno-carcinoma followed with 7.6 per cent. and colloid carcinoma with 1.3 per cent. Graphically, these proportions are well shown in Bar Diagram D. In general, the medullary type was somewhat more rapid in its growth and the tumor as a rule larger on admission, with a slightly diminished frequency of local recurrence, the latter characteristic being probably due to the relative short post-operative longevity associated with this type. In the scirrhous type, on the other hand, there was a higher incidence of local recurrence and a greater post-operative longevity. The

BAR DIAGRAM D

Frequency Distribution of 950 Cases of Carcinoma of the Breast According to the Pathological Diagnosis

Johns Hopkins Hospital (1889–1931)
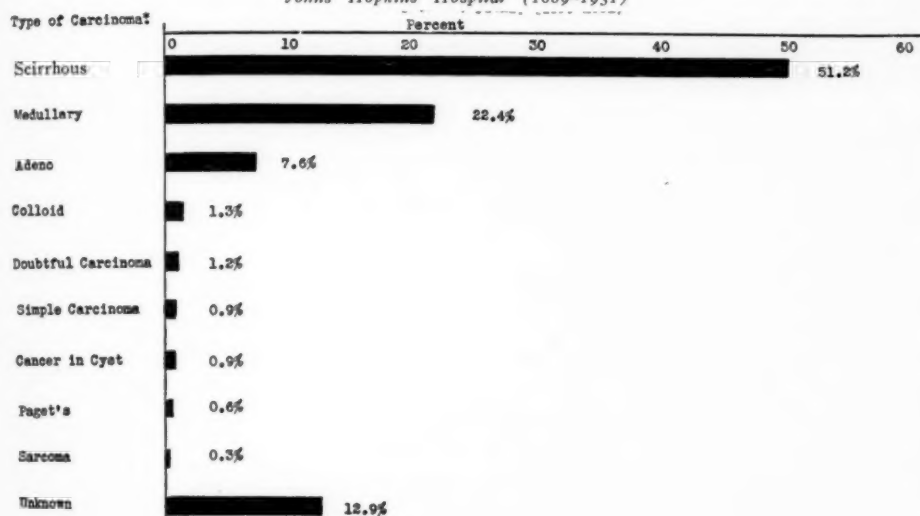
* There was one case (.01 percent) of each of the following types: Colloid-adeno; comedo; intracystic papilloma; papillary carcinoma; scirrhous-adeno and spinal-cell.

adeno- and colloid carcinomata were the most favorable for surgical treatment in that their post-operative life was longer and the recurrences much less. Attention is called to the fact, however, that these various classifications are purely arbitrary and in many instances shade over from one into another. We have a feeling of great uncertainty as to whether or not the biological characteristics of a malignant growth can be prognosticated from an objective histological examination. An example of the futility of such conjectures in our present state of knowledge may be observed in two cases of this series. In one, the tumor was small and had existed for forty years before operation, after which the patient lived for many years. In the other, the tumor was very large and had been present for less than three months. Following operation the patient died from generalized metastases within six months. However, both tumors were infiltrating scirrhous carcinomata indistinguishable in their microscopical pattern. In general, it may be stated for this series of

　
cases that the very cellular types of tumors were as a rule more fulminating and malignant than those less cellular, but attempts to grade the relative malignancy or benignancy to a finer definition proved unsuccessful.

Surgical Treatment.—The main standard by which the operative treatment of carcinoma of the breast may be judged is the cure of the disease locally. The better operation is that one associated with the smallest percentage of local recurrence. The operator cannot be held responsible for undiscoverable metastases, either regional or remote, but should be held to account for a local recurrence. Some confusion has resulted in the past concerning

TABLE XV.—*Frequency Distribution of 950 Cases of Carcinoma of the Breast According to the Pathological Diagnosis*

Johns Hopkins Hospital (1889–1931)

Type of carcinoma	Total no. of cases	Per cent. of cases
Simple	9	.9
Scirrhous	486	51.2
Medullary	213	22.4
Adeno	72	7.6
Paget's	6	.6
Cancer in cyst	9	.9
Colloid	12	1.3
Scirrhous adeno	1	.1
Colloid adeno	1	.1
Comedo	1	.1
Sarcoma	3	.3
Intracystic papilloma	1	.1
Doubtful	11	1.2
Papillary	1	.1
Spinal cell	1	.1
Unknown	123	12.9
Totals	950	99.9

See also Bar Chart D.

the definition of the terms denoting recurrences and metastases, and in order that the standards by which this group of cases were classified may be clearly understood, these terms are defined according to our interpretation. By local recurrence is meant the reappearance of carcinoma at any time following the removal of the primary tumor, by operation, in the operative field, *i.e.*, in the apparent or buried scar. The more radical the operation, the more liberal the interpretation of the term, local recurrence. Regardless of the number of years that have elapsed since the primary operation, a return of carcinoma within the limits of the operative field should be considered a reoccurrence of the primary tumor and not a growth *de novo*. We have observed a local recurrence in the scar following an operative procedure over twenty years after the primary operation, and others after five, ten to fifteen

years. It would seem likely that these local recurrences indicate growths either from inoculations of the operative field with carcinoma at the operation, or regional extensions from the primary growth, and therefore in either event represent a continuation of the disease in that region uninterrupted by the operative procedure. Why their growth is so retarded after transplantation from the primary tumor to a new environment is difficult to determine. It is, of course, possible that the primary growth was equally slow before the patient became aware of its presence. Again, carcinoma seems to grow less rapidly in certain tissues, notably skin, as evidenced by the slow growth of lenticular skin metastases from a rapidly growing primary tumor. We have dropped the term *regional recurrence* for *regional metastases*. It was felt that involvement of the regional glands, *i.e.*, supraclavicular or mediastinal, involvement of the opposite breast, or the skin in the immediate environment, was due undoubtedly to regional metastases. The term, *remote metastases*,

TABLE XVI.—*Frequency Distribution of 950 Cases of Carcinoma of the Breast as to With or Without Metastases at Time of Operation*

Johns Hopkins Hospital (1889–1931)

Metastases	Total no. of cases	Per cent. of cases
With metastases at the time of operation...........	678	71.4
Without metastases at the time of operation........	183	19.3
Unknown.......................................	89	9.4
Totals...	950	100.1

These figures were arrived at by a study not only of the physical examination of each of the patients but also the operative and pathological findings as well. As would be expected a large number of patients had regional metastases that were unsuspected clinically.

includes all metastatic growths far removed from the region of the operative field.

Longevity is also one of the criteria by which to judge the worth of an operative procedure, but not, it would appear, as important as the question of local recurrence. The reasons for this are obvious ones, among them being death from other causes that prevent the patient from living long enough to have a recurrence. It also is well known that in some unusual cases of breast tumors that have not been operated upon the patients have lived for years, one known to us for twenty-five years, her death being due to old age with senile changes. So that in at least a small percentage of cases interruption of the growth by a surgical procedure does not necessarily mean a successful curative operation. Again, it is surprising how long some patients have lived with one or more local recurrences, the carcinoma thus having an uninterrupted continuity.

Patients operated upon late in life when their normal expectancy has been almost completed will die of senile changes, although there may or may not be a complete obliteration and local cure of the carcinoma. Thus the later in life the patient is operated upon the shorter the normal life expectancy and also the post-operative longevity. So that in this group of patients longevity

TABLE XVII.—*Duration of Life in Years; the Absolute Number of Patients That Died within Various Years after an Operation for Carcinoma of the Breast; the Per Cent. of Patients Dead in Each Period; the Per Cent. Alive in Each Period*

Johns Hopkins Hospital (1889–1931)

Length of life	The absolute no. of patients who died in each period	Per cent. of patients who died in each period	Per cent. of patients alive in each period
In hospital.............	25	6.4	93.6
6 months or less.......	69	17.6	82.4
1 year or less..........	127	32.3	67.7
2 years or less.........	225	57.3	42.7
3 years or less.........	269	68.4	31.6
4 years or less.........	306	77.9	22.1
5 years or less.........	322	81.9	18.1
6 years or less.........	338	86.0	14.0
7 years or less.........	351	89.3	10.7
8 years or less.........	360	91.6	8.4
9 years or less.........	364	92.6	7.4
10–14 years or less.....	377	95.9	4.1
15–19 years or less.....	382	97.2	2.8
20–24 years or less.....	390	99.2	.8
25–29 years or less.....	391	99.5	.5
30–32 years or less.....	393	100.0	.0
Totals................	393*	100.0	.0

* Length of post-operative life unknown in twenty-seven cases.

This table is made from the group of 420 patients who comprised the series of known dead. It is to be noted that this chart is cumulative, that is, all the patients and the per cents. of previous years are added on for each specific year group. That is, in the five-year group there are included all the deaths which occurred not only in the hospital but those which occurred in six months or less, one year, two years, three years, four years, and also during the fifth year. Thus by the end of the fifth year 322 patients or 81.9 per cent. had succumbed while 18.1 per cent. remained alive. Attention is called to the fact that each year up to the end of the second year the mortality per year increases quite pronouncedly but diminishes after the second year. In other words, if the patient survives the first two years his chances of living are much improved. See Graphs E and F.

would be a very unreliable index to the efficacy of a surgical procedure. Further, the merits of an operative procedure cannot be correctly ascertained if the affection for which it is applied is of too long standing and too extensive. It is to be noted that in this series of cases a large majority of the patients were in the public ward and in over 53 per cent. of these the tumors were

CANCER OF THE BREAST

large and 71.4 per cent. had regional metastases at the time of operation. (Table XVI.)

An analysis of the ultimate results obtained by the surgical treatment of carcinoma of the breast in this series of 420 cases comprising the known dead group is shown in Table XVII Graphs E and F. *This includes all types of operative procedures* and *it is observed that the operative mortality was 6.4 per cent.*, twenty-five patients dying as a result of the operation. Of these, seven died of pulmonary embolism, which seems remarkable when one considers that in the majority of cases the axillary vein was manipulated freely. Three succumbed to pneumonia, five died of infected wounds, two of myocardial insufficiency, three of post-operative shock, and in five the cause was unknown. By the end of the second year 225 patients (57.3 per cent.) had died. This is also shown in Table XIX, which is non-cumulative, and in Graph G. The greatest number of deaths occurred not only by, but also in, the second year, but after this the mortality per year fell off quite rapidly. Again referring to Table XVII, it is to be noted that by the end of five years 81.9 per cent. had died, leaving 18.1 per cent. alive. In the 420 patients known to be dead the greatest length of life was thirty-two years, to which period two patients survived. One operated upon by Doctor Halsted in 1895 at the age of fifty-four succumbed, at the age of eighty-six, to carcinoma of the liver without any local recurrence. The other was operated upon by Doctor Cushing in 1898 at the age of forty-five and died at the age of seventy-seven of some cause unknown. Undoubtedly, as will be shown, the majority of these patients died of or with carcinoma present but possibly some, particularly the older ones, succumbed from other causes.

A comparison of the types of operations performed in this series of 950 cases, as to post-operative longevity, is of more than usual interest because of the fact that there have been very pronounced opinions in this clinic as to the efficacy of one type of operative procedure in comparison with the other. The complete operation described and performed by Doctor Halsted differed primarily in the removal of a much larger area of skin with the subsequent defect repaired by grafting, more frequently by the use of the Thiersch, occasionally with Reverdin grafts. The radical operation performed by others allowed sufficient skin to remain in order that the various incisions might be closed without grafting. In this study the former have been designated as *Thiersch graft* and the latter as *closed plastic operations.* From Tables XVIII and XIX and Graph G a comparison of the results of the two operative procedures may be observed, for the group of 413 patients of the known dead series. Three hundred three patients were operated upon by the Halsted Thiersch graft method and 106 cases by the closed plastic, while in four Reverdin grafts were used. This is a ratio of about 3:1 in favor of the Thiersch graft operation. From columns four and five, Table XIX, the average length of life following a Thiersch graft and closed plastic operation was calculated and found to be 3.82 years for the former and 3.15 for the

23   353
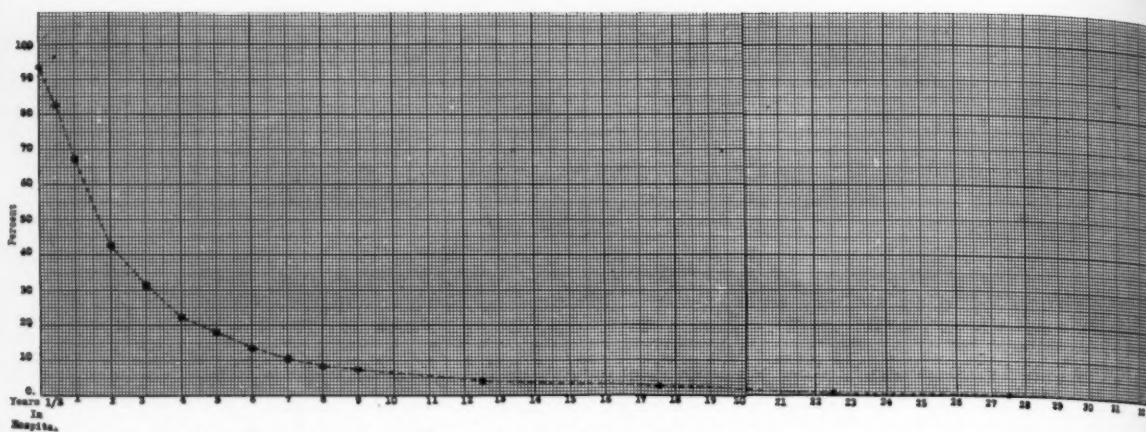
GRAPH E.—Years of post-operative life. Showing the percent of patients having carcinoma of the breast that were alive in each successive year.
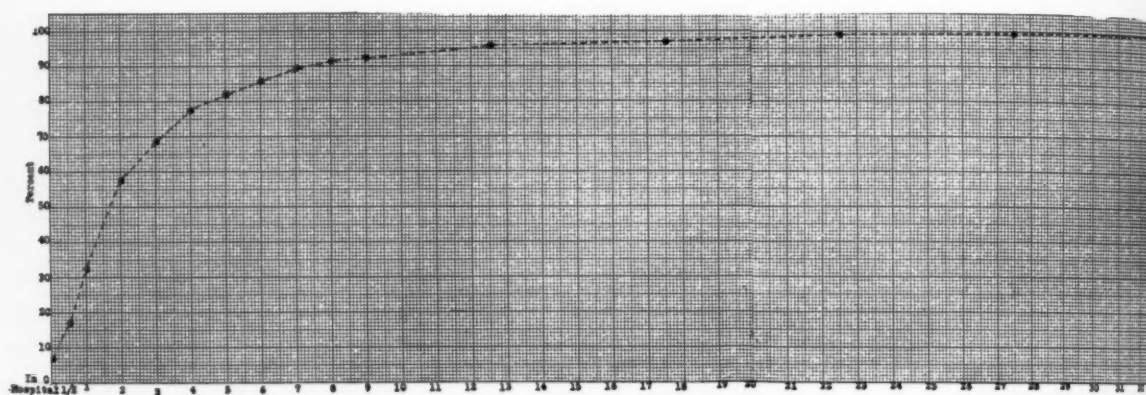
GRAPH F.—Years of post-operative life, showing the total percent of patients having carcinoma of the breast that had died by the end of each successive year.
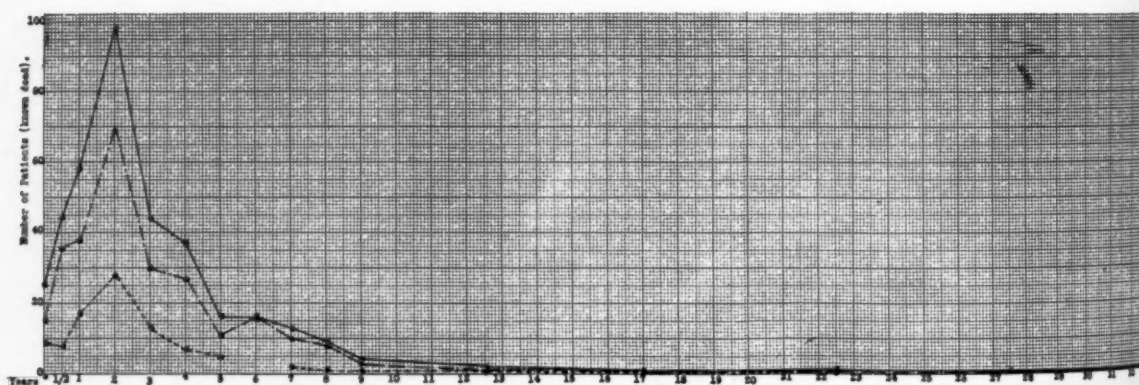
GRAPH G.—Diagram showing length of life after an operation for carcinoma of the breast, closed plastic operation — — — — . Thiersch graft operation — . — . — . — . — . Both types of operation. ——— * In hospital.

latter—a difference of 0.67 of a year or practically eight months in favor of the Thiersch graft procedure, which, although small, is a definite difference. It is to be noted that if one included in the Halsted Thiersch graft group the cases in which Reverdin grafts were used, the difference in longevity would be even more in favor of the type of operation in which grafting has been made necessary by the large sacrifice of skin, as in the Thiersch graft group. This difference in longevity is essentially negative from a statistical point of view, but when one takes into consideration the fact that the Thiersch graft operation was performed previous to 1925 on by far the greater majority of public-ward cases in which the disease was very extensive, and, as a rule, of long duration, whereas the closed plastic procedure was performed to a large extent on private patients in whom the tumors were usually smaller and the

TABLE XVIII.—*Frequency Distribution of 950 Cases of Carcinoma of the Breast as to Type of Operation*

Johns Hopkins Hospital (1889–1931)

Type of operation	Total no. of cases	Per cent. of cases
Complete, Thiersch graft.....	524	55.2
Complete, closed plastic......	274	28.8
Reverdin graft..............	4	.4
Incomplete operation.........	40	4.2
Not treated................	72	7.6
Inoperable.................	29	3.1
Arm amputation.............	2	.2
Type unknown..............	5	.5
Totals.....................	950	100.0

See Graph G.

disease less extensive, one realizes that the Halsted Thiersch graft procedure has stood a more severe test, and achieved more than the figures 0.67 would denote. Attention is also called to the fact that those favoring the closed plastic procedure resorted to grafting only when the malady was so extensive as not to admit of a plastic closure. For this reason, all the unfavorable cases were relegated to the Thiersch graft operation. It should also be stated that the follow-up examination of the patients submitted to the Halsted Thiersch graft operation, due to the persistent efforts of Doctors Bloodgood and Halsted, has been much more active and thorough than with the closed plastic cases. Thus in the former group unfavorable developments were more accurately detected and recorded. In the last six years, closed plastic operations have been performed to a large extent on public-ward patients who have not lived long enough in the majority of instances to have died of the disease, *i.e.*, through the crucial two-year period, or to have developed complications, whereas the opposite is true for the Thiersch graft group. By this is meant

TABLE XIX.—*Frequency Distribution of 420 Cases (Known Dead) Showing the Length of Life after Operation for Carcinoma of the Breast*
Johns Hopkins Hospital (1889–1931)

Length of life after oper.	Type of Operation					Total No. patients dead, operated on for carc. breast	Per cent. patients dead
	Type of oper. unknown	No. patients having Reverdin graft	No. patients dead, having arm amputation	No. patients dead, having complete Thiersch graft	No. patients dead, having complete closed plastic		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
In hospital	1 (inoperable)			15	9	25	6.0
Six months or less				36	8	44	10.5
During 1st year		2	1	38	17	58	13.8
During 2nd year				70	28	98	23.3
During 3rd year	1			30	13	44	10.5
During 4th year	2	1		27	7	37	8.8
During 5th year				11	5	16	3.8
During 6th year				16	—	16	3.8
During 7th year	1			10	2	13	3.1
During 8th year				8	1	9	2.1
During 9th year				3	1	4	1.0
10th to 14th year				7	6	13	3.1
15th to 19th year		1		3	1	5	1.2
20th to 24th year				7	1	8	1.9
25th to 29th year				1		1	.2
30th to 34th year				2		2	.5
Unknown	1			19	7	27	6.4
Total	6	4	1	303	106	420	100.0

This table is not cumulative and demonstrates the post-operative longevity in the different years following operations of both the Thiersch graft and the closed plastic types. The second year, as shown by Graph G, was the year in which the greatest number of deaths occurred. Following this the mortality per year fell off very rapidly from 23.3 per cent. in the second year to 10.5 per cent. in the third, 8.8 per cent. in the fourth, *etc.* These figures are plotted in a straight line, the top curve of Graph G. From this point on the data are collected in five-year periods because of the scarcity of cases. This table also demonstrates the relative merits of the two operative procedures. Three hundred and three were operated upon by the Halsted Thiersch graft method and 106 by the closed plastic. The ratio of the Thiersch graft to the closed plastic procedure is about 3 : 1. From columns 4 and 5 the average length of life following the Thiersch graft and the closed plastic operation is calculated and found to be 3.82 years for the former and 3.15 for the latter.

that the very few patients having been so operated upon by this latter method since 1925 have had at least six years of post-operative life and freedom from a local recurrence. Statistically, these recent cases since 1925 are a distinct

TABLE XX.—*Number of Operations for Carcinoma of the Breast Performed by Various Surgeons at the Johns Hopkins Hospital, and the Number of Cases Where There Was a Local Recurrence (1889–1931)*

Operator	No. of operations	No. of local recurrences	Per cent. local recurrences
A	215	48	22.3
B	132	28	21.2
C	46	8	17.4
D	22	7	31.8
E	39	3	7.7
F	17	5	29.4
G	24	5	20.8
H	5	1	20.0
I	32	6	18.8
J	19	2	10.5
K	25	6	24.0
L	36	4	11.1
M	34	3	8.8
N	3	—	—
O	12	—	—
P	20	5	25.0
Q	19	2	10.5
R	36	2	5.6
S	11	—	—
T	1	—	—
U	16	1	6.3
V	19	2	10.5
W			
X	9	—	—
Y	4	—	—
Z	11	—	—
Aa	8	1	12.5
Bb	5	3	60.0
Cc	1	—	—
Dd	1	—	—
Ee	4	—	—
Ff	3	—	—
Gg	4	1	25.0
Hh	1	1	100.0
Ii	1	—	—
Jj	1	—	—
Kk	1	—	—
Ll	1	—	—
Mm	1	—	—
Not treated	72		
Omitted	39		
Totals	950	144	

advantage in favor of the closed plastic group, but show rather to the disadvantage of the Halsted Thiersch graft series. These points are brought out because the field of usefulness in surgery of numerical or statistical computations is quite limited owing to the great variation in the type of patient as well as the extent of the disease. It also should be considered in the light of all possible information which may have some bearing on the circumstances involved. As stated before, however, longevity is only one of the criteria by which an operative procedure for the cure of carcinoma of the breast should be judged. It is felt that this series of 413 cases, in which the post-operative length of life is known, is a fairly good test of both operative procedures, for the cases extend over a period of forty-two years and were dealt with by surgeons who performed the radical removal of the breast together with the pectoral muscles and axillary contents in essentially the same manner. They differed only in the amount of skin removed with the breast and therefore in the method of closure. The list of operators is given in Table XX. *A comparative study of the two operative procedures with reference to the yearly death rate,* using the cumulative method, may be seen in Table XXI. In each period, excepting six months, eight and nine years, respectively, the percentage of patients who died after the Halsted Thiersch graft operation is smaller for each successive period than after the closed plastic operation. In these periods noted, *i.e.,* six months, eight and nine years, the difference in the percentage of deaths was negligible. The main difference is from the first year through the fifth, when per year there are fewer dying after the Halsted Thiersch graft than after the closed plastic operation, or a greater percentage of patients submitted to the Thiersch graft operation for carcinoma of the breast will live through the first five years than those on whom a closed plastic operation was performed. However, from the sixth year on the difference in the percentage living is practically negligible. In those who have lived five years the longevity is unaffected by the type of operation. As will be shown later, the higher yearly mortality for the closed plastic operation during the first five years is probably due to the effect of local recurrences which occur and run their course within that period of time. By the end of twenty-four years all of those operated upon by the closed plastic method had died, whereas it was not until the end of the thirty-second year following operation that the last patient died who had been operated upon by the Thiersch graft method. It is to be said that this difference in the total longevity following the two operative procedures was caused by the long life of only three patients. Their total length of post-operative life was ninety-one years, which would increase the average length of life of the entire Thiersch graft group approximately one-third of a year, or four months. These are graphically shown in Chart H. It may, therefore, be suggested that in this group the chances of a patient to live through the five-year period were greater if they had a larger area of skin removed and with the closure made by grafting than if a plastic operative procedure was employed.

After five years their chances of surviving were about equal for the two operative procedures.

The effect on post-operative length of life of regional metastases, i.e., axillary and supraclavicular glands of the same side, is shown in Table XXII. Of

TABLE XXI.—*Frequency Distribution of 409 Cases (Known Dead) of Carcinoma of the Breast Showing the Length of Life after Thiersch Graft Operations and after Closed Plastic Operations*

Johns Hopkins Hospital (1889–1931)

Length of life after oper.	Cases of Thiersch graft oper. cumulative	Cases of closed plastic cumulative	Per cent. Thiersch graft	Per cent. closed plastic
In hospital.	15	9	5.3	9.1
6 months or less.	51	17	18.0	17.2
1 year or less.	89	34	31.3	34.3
2 years or less.	159	62	56.0	62.6
3 years or less.	189	75	66.5	75.8
4 years or less.	216	82	76.1	82.8
5 years or less.	227	87	79.9	87.9
6 years or less.	243	87	85.6	87.9
7 years or less.	253	89	89.1	89.9
8 years or less.	261	90	91.9	90.9
9 years or less.	264	91	92.9	91.9
10–14 years or less.	271	97	95.4	98.0
15–19 years or less.	274	98	96.5	99.0
20–24 years or less.	281	99	98.9	100.0
25–29 years or less.	282	—	99.2	—
30–34 years or less.	284	—	100.0	—
Totals.	284	99		

A comparative cumulative study of the length of life following operation by the two procedures has been made in a similar series of the known dead analyzed in Table XIX consisting of 303 cases operated on by the Halsted Thiersch graft and 106 by the closed plastic, eliminating 11 cases because in 5 the type of operation was unknown. Four were Reverdin grafts, one was inoperable, and an arm was amputated in one. The percentage of patients dying after the Halsted Thiersch graft operation is smaller and therefore the percentage of patients living is greater for each successive period than following the closed plastic operation with the exception of the periods, six months and eight and nine years. In these latter instances the difference in the percentage of cases dying following the two operative procedures is negligible. The greatest difference in the per cents. of those dying after the two types of operations is between the first and fifth year, which difference favors the Thiersch graft. From the seventh year on the difference in the percentage of those dying is never greater than two. From the sixth year on the difference in the percentage living following the two procedures is negligible. This is graphically shown by Chart H.

the group of 420 known dead 379 cases were available for study, the data being insufficient in forty-one cases. It is interesting to note that twenty-three patients having regional metastases died in the hospital following operation,

whereas not a single case without metastases contributed to the immediate operative mortality. It is to be recalled that out of the entire group of 950 cases there were only twenty-five deaths in the hospital. Thus, in all but two cases, concerning which there were insufficient data, of the group constituting the hospital or operative mortality, there were regional metastases. This may be explained not only by the fact that patients with extensive metastases are as a rule poorer operative risks but also by the fact that in these cases the difficulties of dissection are markedly increased, thus prolonging the operative procedure. Of this group of 379 patients, 326 had metastases and

TABLE XXII.—*A Classification of 379 Cases of Carcinoma of Breast as to the Length of Post-operative Life and the Presence and Absence of Regional Metastases (All These Patients Are Known to Be Dead)*

Length of post-oper. life	With metastases (1)	Without metastases (2)	Total
In hospital	23	—	23
6 months	41	2	43
1 year	51	4	55
2 years	89	9	98
3 years	34	9	43
4 years	28	5	33
5–9 years	43	13	56
10–14 years	7	6	13
15–19 years	4	—	4
20–24 years	4	4	8
25–29 years	—	1	1
30–34 years	2	—	2
Totals	326	53	379

Of the 420 dead, forty-one cases were eliminated because of insufficient data, leaving 379 for examination. The ratio of patients with metastases to those without is 6 : 1 :: 326 : 53. This ratio is not maintained but markedly increased for those cases with metastases during the first two years, dropping after the completion of the second year. It is evident that about two-thirds of the patients with metastases have died by the end of the second year while less than one-third of those not having metastases have succumbed at this time.

fifty-three were found to be free from them, a ratio of 6 : 1. It would be expected that this ratio of 6 : 1 should be maintained in the yearly death rate if the metastases *per se* played no rôle in the post-operative longevity. This, however, is found not to be true. The ratio of 6 : 1 is not borne out but markedly increased for these cases with metastases during the first two years, dropping after the end of the second year. As shown previously, 71.4 per cent. of the patients of this series have had regional metastases at the time of operation. It can be seen at a glance in Table XXII that about two-thirds of the patients with metastases have died by the end of the second year, while less than one-third of those not having regional metastases have

TABLE XXIII.—*Showing the Length of Life after an Operation for Carcinoma of the Breast; (a) Having Either a Thiersch Graft or Closed Plastic Operation; (b) With or without Metastases at the Time of the Operation. The Number of Patients is given in Absolute Numbers and in Percentages*

Johns Hopkins Hospital (1889–1931)

No. of yrs. alive	Thiersch graft				Closed plastic				Thiersch graft				Closed plastic			
	With metastases		Without metastases		With metastases		Without metastases		With metastases		Without metastases		With metastases		Without metastases	
	No. cases	Per cent.	No. cases	Per cent.	No. cases	Per cent.	No. cases	Per cent.	No. cases	Per cent.	No. cases	Per cent.	No. cases	Per cent.	No. cases	Per cent.
Unknown	18	6.8	1	2.9	7	8.1	—	—	—	—	—	—	—	—	—	—
In hospital	15	5.7	—	—	8	9.3	—	—	—	—	—	—	—	—	—	—
6 months	33	12.5	2	5.7	8	9.3	—	—	—	—	—	—	—	—	—	—
1 year	34	12.8	4	11.4	17	19.8	—	—	—	—	—	—	—	—	—	—
2 years	67	25.3	3	8.6	22	25.6	6	31.6	1	4.5	1	4.0	4	16.7	1	3.8
3 years	25	9.4	5	14.3	9	10.5	4	21.1	2	9.1	1	4.0	3	12.5	3	11.5
4 years	22	8.3	4	11.4	6	7.0	1	5.3	2	9.1	1	4.0	—	—	1	3.8
5–9 years	37	14.0	10	28.6	6	7.0	3	15.8	5	22.7	11	44.0	6	25.2	4	15.4
10–14 years	5	1.9	2	5.7	2	2.3	4	21.1	3	13.6	4	16.0	7	29.2	9	34.6
15–19 years	3	1.1	—	—	1	1.1	—	—	5	22.7	4	16.0	2	8.3	3	11.5
20–24 years	4	1.5	—	—	—	—	1	5.3	5	22.7	4	16.0	1	4.2	4	15.4
25–29 years	—	—	3	8.6	—	—	—	—	—	—	—	—	—	—	1	3.8
30–34 years	2	.8	1	2.9	—	—	—	—	—	—	—	—	—	—	—	—
Totals	265	300	35	405	86	105	19	502	22	47	25	97	24	50	26	

This table includes not only the known dead but the well, of which there are ninety-seven cases. The total thus comes to 517 but fifteen cases were omitted from the chart because in four of these it was not known whether the patient had metastases at the time of operation. In five cases the type of operation was not known. Two were inoperable because of the very extensive involvement of the breast together with a great lymphoedema of the arm, which was amputated as a palliative measure. In four cases Reverdin grafts were used. "X" in the table means the length of life following operation was unknown. The total number of cases in each group is given at the end of each division, thus the dead and living are separated to be again divided into two main groups, *i.e.*, those having the Thiersch graft and the closed plastic operations. These are further divided with reference to regional metastases.

succumbed by this time. It would seem likely, therefore, that the high mortality of 57.3 per cent. for the group as a whole, occurring at the end of the second year, is in a major part due to the high death rate of those having regional metastases at the time of operation.

A comparative study was made of the relative merits of the closed plastic and the Halsted Thiersch graft operations in regard to the post-operative longevity of these patients, with and without regional metastases. For this study the group of patients constituting the living and known dead were used,

TABLE XXIV.—*Showing the Number of Patients, the Per Cent. Dead and the Per Cent. Alive in Various Durations of Life after an Operation for Carcinoma of the Breast;* (a) *Having Either a Thiersch Graft or Closed Plastic Operation;* (b) *With Metastases. All These Patients Are Known to be Dead*

Johns Hopkins Hospital (1889–1931)

| | With metastases | | | | | |
| | Thiersch graft | | | Closed plastic | | |
Length of life after operation	No. of patients	Per cent. dead	Per cent. alive	No. of patients	Per cent. dead	Per cent alive
In hospital............	15	5.3	94.7	8	9.3	90.7
6 months or less......	48	18.1	81.9	16	18.6	81.4
1 year or less.........	82	30.9	69.1	33	38.4	61.6
2 years or less........	149	56.2	43.8	55	64.0	36.0
3 years or less........	174	65.7	34.3	64	74.4	25.6
4 years or less........	196	74.0	26.0	70	81.4	18.6
5–9 years or less......	233	87.9	12.1	76	88.4	11.6
10–14 years or less....	238	89.8	10.2	78	90.7	9.3
15–19 years or less....	241	90.9	9.1	79	91.9	8.1
20–24 years or less....	245	92.5	7.5	—	—	—
25–29 years or less....	—	—	—	—	—	—
30–34 years or less....	247	93.2	6.8	—	—	—
Unknown............	18	6.8	—	7	8.1	—

This table is cumulative and demonstrates the relative merits of the two operative procedures for the 326 patients known to be dead in whom there were regional metastases. It is to be noted that in the Thiersch graft group the percentage dying in each successive year is lower than the percentage dying in the closed plastic group.

giving a total of 502 cases, after removing fifteen patients concerning whom there were insufficient data. In Table XXIII it may be noted that of the known dead, 405 patients having regional metastases before operation, the percentage of patients that have died in the succeeding year following operation was approximately the same after the two operative procedures. Of this same group of known dead in whom there were no regional metastases previous to operation, the percentage dying by the end of the second and third years was lower for the Halsted Thiersch graft group than the closed

plastic, but higher for the period of four to nine years and again lower for the ten to fourteen years. Again, it is to be noted that over 50 per cent. of the patients in this group that have been operated upon were dead by the completion of the second year and of this group the majority succumbing by this time had been operated upon by the closed plastic method. For the ninety-seven patients living it is to be noted that a greater number of patients have lived a greater number of years in the Thiersch graft group than in

TABLE XXV.—*Showing the Number of Patients, the Per Cent. Dead and the Per Cent. Alive in Various Durations of Life after an Operation for Carcinoma of the Breast; (a) Having Either a Thiersch Graft or Closed Plastic Operation; (b) Without Metastases. All of these Patients Are Known to be Dead*

Johns Hopkins Hospital (1889–1931)

| | Without metastases | | | | | |
| | Thiersch graft | | | Closed plastic | | |
No. of yrs. alive after operation	No. of patients	Per cent. dead	Per cent. alive	No. of patients	Per cent. dead	Per cent. alive
In hospital..........	—	—	—	—	—	—
6 months or less......	2	5.7	94.3	—	—	—
1 year or less.........	6	17.1	82.9	—	—	—
2 years or less........	9	25.7	74.2	6	31.6	68.4
3 years or less........	14	40.0	60.0	10	52.6	47.4
4 years or less........	18	51.4	48.6	11	57.9	42.1
5–9 years or less......	28	80.0	20.0	14	73.7	26.3
10–14 years or less....	30	85.7	14.3	18	94.7	5.3
15–19 years or less....	—	—	—	—	—	—
20–24 years or less....	33	94.3	5.7	19	100.0	—
25–29 years or less....	34	97.1	2.9	—	—	—
30–34 years or less....	—	—	—	—	—	—
Unknown............	1	2.9	—	—	—	—

A cumulative table showing the relative merits of the two operative procedures in a group of patients of known dead in whom there were no regional metastases before operation. Attention is called to the fact that in the Thiersch graft group the percentage of patients dying is lower with the exception of the five- to nine-year period than the percentage in the closed plastic.

the closed plastic. This part of Table XXIII should be read from the bottom up. There are more patients living, however, in the closed plastic group, fifty as against forty-seven in the Thiersch graft, but this is due to the fact that the greater number of breast operations since 1925 have been of the closed plastic type, and as yet the patients have not survived the most hazardous earlier years. The cumulative Tables XXIV, XXV and XXVI show the comparative results in better definition. For 326 patients known to be dead in whom there were regional metastases, the percentage of deaths in each
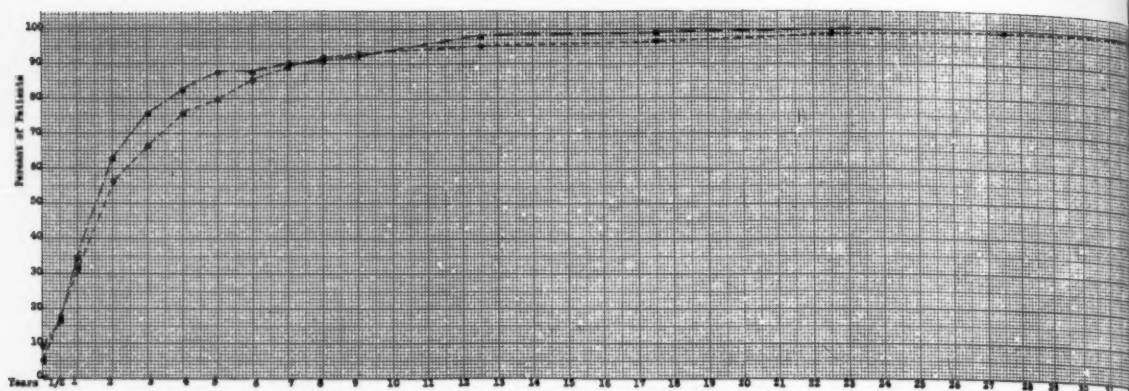
GRAPH H.—The percent of patients operated upon by Thiersch graft —..—..—..— and closed plastic — — — — — Methods in carcinoma of the breast who died during the first year; during the first two years, *etc.* * In hospital.
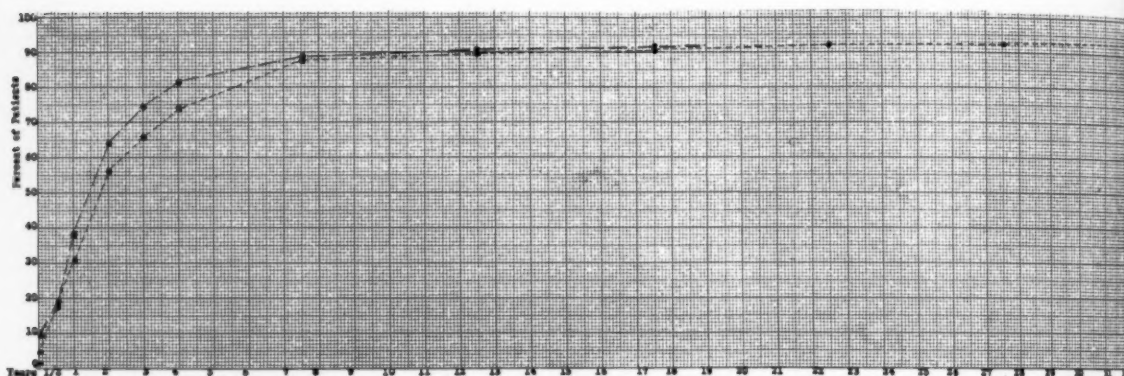
GRAPH I.—A comparison of the percents of those patients who had died by the end of each successive year. Thiersch graft — — — — —, closed plastic —..—..—..—, both with metastases. * In hospital.
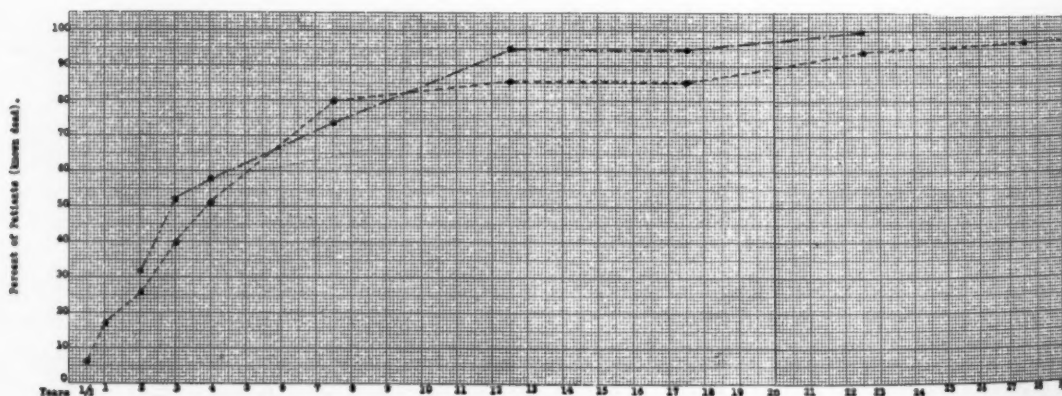
GRAPH J.—A comparison of the percent of those patients who had died by the end of each successive year. Thiersch graft — — — — —, closed plastic —..—..—..—, both without metastases.

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successive year is lower for the Halsted Thiersch graft than the closed plastic group. The same may be said for the series without metastases except for the five- to nine-year period. In the group of those living at present there are forty-seven in the Halsted Thiersch graft group and fifty in the closed plastic group, and in spite of this slight numerical disadvantage there are a greater number of patients living a longer period of years in the Thiersch graft group than in the closed plastic group. (Graphs I and J.)

TABLE XXVI.—*Showing the Number of Patients and the Per Cent. Alive in Various Durations of Life after an Operation for Carcinoma of the Breast.* (a) *Having Either a Thiersch Graft or Closed Plastic Operation;* (b) *With or Without Metastases.*
These Patients Are Known to be Well

Johns Hopkins Hospital (1889–1931)

| No. of yrs. alive after operation | With metastases | | | | Without metastases | | | |
| | Thiersch graft | | Closed plastic | | Thiersch graft | | Closed plastic | |
	No. of pts.	Per cent. pts.	No. of pts.	Per cent. pts.	No. of pts.	Per cent. pts.	No. of pts.	Per cent. pts.
25–29 years	1	4.5	—	—	2	8.0	1	3.8
20–24 years	2	9.1	—	—	6	24.0	1	3.8
15–19 years	7	31.8	1	4.2	8	32.0	5	19.2
10–14 years	10	45.5	3	12.5	12	48.0	8	30.8
5–9 years	15	68.1	10	41.7	23	92.0	17	65.4
4 years	17	77.3	16	66.7	24	96.0	21	80.8
3 years	19	86.4	17	70.8	24	96.0	21	80.8
2 years	21	95.4	17	70.8	25	100.0	22	84.6
1 year	22	100.0	20	83.3	—	—	25	96.2
6 months	—	—	24	100.0	—	—	26	100.0
Totals	22	100.0	24	100.0	25	100.0	26	100.0

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There are forty-six patients of the Thiersch graft group living at present and fifty-one of the closed plastic. In spite of this slight numerical disadvantage there are a greater number of the patients living a longer number of years in the Thiersch graft than in the closed plastic. See Graphs I and J.

An analysis of the operative results in regard to the length of life following operation was made for each year in order to determine whether the efficacy of the operative procedures varied from year to year and also whether the length of post-operative life was shorter when the patients came to operation late in the stage of the disease, as they did in the earlier years of the Johns Hopkins Hospital. In Table XXVII is recorded the average

length of life following operation for the successive years from 1889 until 1931. The average length of life is computed on the basis of the 420 cases of known dead. In the adjoining column the total number of patients is given, but in this tabulation those living and lost to record could obviously not be used. The total number of years that those known to have died still lived was estimated and the average length of life computed by division of this number by the number of deceased. It is to be noted that in 1895, 1898, and 1903 the average length of life was longer than in other years. From 1909 on to date, 1931, the average post-operative length of life begins to decline. Especially is this true for the most recent years, but this is partly due to the fact that a larger percentage of those operated upon previous to 1909 have died and the maximum duration of life in these cases is known. In the earlier years the average length of life is of necessity greater because those patients that have had an opportunity to live a greater number of years and then died have increased the average length of life for the group of those years. The converse explains the shorter average length of life for the groups of the more recent years since 1909. Therefore, from a statistical standpoint, a larger number of cases necessarily dealt with present a more accurate result. With the exception of this general trend downward from 1909 on there is no constant tendency which could be attributed to operative skill. In the earlier years, when practically only the Halsted Thiersch graft operation was used, there is a pronounced fluctuation in the average length of life for the various years in spite of the fact that the duration of life is known in a large percentage of cases. For instance, in 1892, 1893, 1897, 1901 and 1902, the average length of life was quite short regardless of the fact that the treatment and type of operation were exactly the same, and in the majority of cases were in the hands of the same operator, as in the years 1895, 1898, 1899 and 1903, in which the maximum length of life following operation was attained. This would seem to indicate that there will be marked fluctuations in the post-operative results, in spite of the constancy of operative method and individual skill, depending on the type of tumor and the extent of the disease.

In Table XXVIII the average length of life for patients of the known dead group who were operated upon is shown for each decade. The first decade, 1890 to 1899, was computed and the average length of life was found to be 4.57 years, which proved to be the same as for the eleven-year period from 1889 to 1899. There was only one additional case for 1889. It is quite interesting to observe that the average length of life from 1889 to 1910 was much greater than from 1910 to the present. As stated, part of this is due to the fact that those operated on between 1889 and 1900 have had an opportunity to live longer, but that does not suffice to explain the rather sudden decline in the average post-operative length of life from 1910 on. For instance, in the decade from 1890 to 1899, 68 per cent. of the total number of patients had died and the average length of life for this group was 4.57 years. From 1900 to 1909, 53 per cent. of the total number of patients had

TABLE XXVII.—*Average Length of Life for Known Dead Following Operation for Carcinoma of the Breast for the Successive Years, 1889–1931*

Years	No. of known dead	No. of cases	Length of life X	Total no. yrs. all lived	Average length of life
1889	2	6	1	4	4.00
1890	5	14		15	3.00
1891	8	11		30	3.75
1892	12	21		34	2.83
1893	7	10		23	3.29
1894	19	24		86½	4.55
1895	16	22	1	97	6.46
1896	17	22		58½	3.44
1897	19	23		53	2.79
1898	22	30		143	6.50
1899	16	27	1	91	6.07
1900	11	21		63½	5.77
1901	17	20	1	46	2.88
1902	16	22		48½	3.03
1903	15	25	1	87	6.21
1904	12	27		49	4.08
1905	13	27	1	56½	4.71
1906	9	20	2	28½	4.07
1907	17	29	2	74½	4.97
1908	12	23	1	48	4.36
1909	12	23		41	3.43
1910	18	23		55	3.06
1911	15	27		43½	2.90
1912	13	22		32	2.46
1913	6	14	1	10½	2.10
1914	13	28		29½	2.27
1915	6	23	1	29	5.08
1916	7	21		21½	3.07
1917	10	25		23	2.30
1918	4	19		11½	2.88
1919	9	29		21	2.33
1920	9	26		37	4.11
1921	5	29		6½	1.3
1922	4	16		3	.75
1923	2	22		3	1.50
1924	3	29		13	4.33
1925	3	18		8	2.67
1926	4	28	1	2	.67
1927	7	24		12½	1.8
1928	2	21		2	1
1929	1	20		2	2
1930	2	31		Both in hosp.	0
1931		8			
Total	420				

The total number of years the known dead lived was estimated and the average length of life computed by division of this number by the number of dead. It is to be noted that in 1895, 1898, 1899 and 1903 the average length of life was larger than in other years. From 1909 on to date, 1931, the average length of post-operative life begins to decline. Especially is this true for the most recent years. Undoubtedly this is due to the fact that a lot of those operated upon previous to 1909 have died and the maximum duration of life in these cases is known. The average age of the patient on admission to the hospital from 1889 to 1909 was 49.52 years, whereas the average age from 1910 to 1931 is 49.12 years of age.

died with an average length of life of 4.31 years. Thus 15 per cent. less had died in this decade and it made a difference in the average length of life for that decade of only .26 of a year. Therefore, the sudden drop in the average length of post-operative life for the decade from 1910 to 1919 of 1.51 years is not likely to be entirely accounted for by the fact that this is a more recent decade, for 43 per cent. of the total number of patients have died, making a difference of only 10 per cent. between this decade and the

TABLE XXVIII.—*Average Post-operative Length of Life of Patients Having Carcinoma of the Breast; by Decades*

Johns Hopkins Hospital (1889–1931)

Years	Per cent. of patients dead	No. of patients dead	Yrs. of life after operation	Average length of life after operation (in yrs.)
1890–1899............	68	138	631	4.57
1889–1899............		139	635	4.57
1900–1909............	53	126	543	4.31
1910–1919............	43	99	277	2.80
1920–1929............	17	39	89	2.28
1920–1930............	15	41	89	2.17

In the first decade, 1890–1899, the average length of life was found to be 4.57 years which proved to be the same as for the eleven-year period from 1889 to 1899. The average length of life from 1889 to 1910 was greater than from 1910 to the present. This is due to the fact that those operated upon between 1889 and 1900 have had an opportunity to live longer on the average than those operated on since. From 1890 to 1899, 68 per cent. of the total number of cases had died and the average length of life for this group was 4.57 years. From 1900 to 1909, 53 per cent. of the total number of cases had died with an average length of life of 4.31 years. Thus 15 per cent. less had died in this decade which made a difference in the average length of life for that period of .26 of a year. Therefore, the sudden drop in the average length of life for the decade 1910–1919 of 1.51 years in the average length of post-operative life is more likely to be entirely compensated for by the fact that this is a more recent decade, for 43 per cent. of the total number of cases have died, making a difference of only 10 per cent. between this decade and the previous one, whereas, with a 15 per cent. difference existing between the decades 1899 and 1909 was sufficient to account for only a small fraction of a year. In the succeeding decade, 1920–1929, the percentage of patients dying was 17, whereas the average length of life was 2.28 years. With this drop of 26 per cent. from the preceding decade the difference in the average length of life was .52 years which suggests that the determinable results from 1920–1929 compare favorably with the decade 1900–1910. The same may be stated for the period 1920–1930.

previous one, whereas a 15 per cent. difference existing between the decades 1890–1899, and 1900–1909 was sufficient to account for only a small fraction of one year in post-operative longevity. In the succeeding decade, 1920–1929, the percentage of patients dying was 17, whereas the average length of life was 2.28 years. With this drop of 26 per cent. from the preceding

decade the difference in the average length of life was 77 years, which suggests that the determinable results for the decade 1920–1929 compare favorably with those of the decades preceding 1910. The same may be stated for the eleven-year period of 1920 to 1930. Owing to the fact that by the decade 1910–1919 the treatment of carcinoma of the breast was fairly well standardized in the Johns Hopkins Hospital, except for minor variations in the several operators, a variation that persisted in earlier and later decades as well, demonstrates that there is an inevitable fluctuation in the results of the treatment of breast cancer, due, probably, to the type of neoplasm and the indeterminable extent of the disease.

If now one compares the efficacy of the two types of operation from the standpoint of local recurrence, which, after all, is the best criterion of an operative procedure, again the Halsted Thiersch graft operation appears to have the advantage.

If one includes all the cases of carcinoma of the breast which have been operated upon in the Johns Hopkins Hospital, excepting eighteen cases operated upon in 1931 in which there was no follow-up study, it will be noted that this total comes to 750, and includes 420 known dead, 209 lost track of, ninety-seven living and well, of whom 35 per cent. have been operated upon less than five years, twenty-four well but having a local recurrence. In these 750 cases there were 144 (19.2 per cent.) who had local recurrences. In Table XXIX are computed the number of local recurrences after the different types of operation for patients known to be dead. Of this group of 419 cases local recurrences occurred in 116, 26 per cent. of which followed the Halsted Thiersch graft and 34 per cent. the closed plastic procedure, a difference of 8 per cent. in favor of the former operation. Conversely, 48 per cent. of the patients operated upon by the Halsted Thiersch graft method had no local recurrence to compare with 38.7 per cent. after the closed plastic type of operation. Thus 9.3 per cent. more patients operated upon by the Thiersch graft method had *no* local recurrence and 8 per cent. fewer cases had local recurrences by this method. If only the known dead group of 419 cases, concerning which there are accurate data, is considered together with twenty-eight patients in whom the presence of a local recurrence was known, we have a total of 447 cases, in which there were 144 instances of local recurrence or 32.2 per cent. (Table XXX.) A comparison of the operative results in this group discloses the fact that the incidence of local recurrence is 9.6 per cent. or approximately 10 per cent. less following the Halsted Thiersch graft operation. If the cases with Reverdin grafts were included with the Thiersch graft group the percentage in favor of the latter would be even more pronounced. As a matter of fact, these two groups belong together, for in both a large amount of skin and subcutaneous tissue was sacrificed, differing only in the type of skin graft used to close the remaining skin defect.

In an effort to determine the effect of local recurrence on the post-operative longevity, the computations of the average length of life for the

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TABLE XXIX.—*The Number of Local Recurrences; the Number of No Local Recurrences after Operation of Thiersch Graft, Closed Plastic or Reverdin Graft for Carcinoma of the Breast*

Type of operation	Local recurrence	No local recurrence	No data	Total No. of cases	Per cent. of local recurrence	Per cent. of no local recurrence	Per cent no data
Thiersch graft..................	79	146	79	304	26.0	48.0	26.0
Closed plastic..................	36	41	29	106	34.0	38.7	27.4
Reverdin graft..................		4		4			
Type unknown..................	1	1	3	5			
Totals......................	116	192*	111	419			

* Of the 192 cases where there was no local recurrence, twenty died in the hospital and one immediately afterwards.

Four hundred and nineteen patients of the known dead group were analyzed in this table. One hundred and sixteen had local recurrences, 26 per cent. of which recurred after the Thiersch graft. In 192 cases of this group of 419, or 45.8 per cent., there was no local recurrence. Three hundred and four of the 419 cases were operated on by the Thiersch graft and of these 146 or 48 per cent. had no local recurrence. The results following the use of the closed plastic procedure were as follows: of 106 cases, in 41 or 38.7 per cent., there was no local recurrence. Thus 9.3 per cent. more patients operated upon by the Thiersch graft method had no local recurrence and 8 per cent. fewer cases had a local recurrence.

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CANCER OF THE BREAST

TABLE XXX.—*The Number and Per Cent. of Local Recurrences after Operations for Carcinoma of the Breast, by the Thiersch Graft, Closed Plastic and Reverdin Graft Methods*

Johns Hopkins Hospital (1889–1931)

Type of operation	No. of local recurrences	No. of operations	Per cent. of local recurrences
Thiersch graft............	97	322	30.1
Closed plastic............	46	116	39.7
Reverdin graft............	—	4	—
Type unknown...........	1	5	20.0
Totals...................	144	447	32.2

In this table are included not only 419 of the known dead group but 28 patients that are living and have had a local recurrence. The total number of cases in this group comes to 447. 144 or 32.2 per cent. had local recurrences. 322 were operated on by the Thiersch graft method and 97 or 30.1 per cent. had local recurrences. Of 116 cases, 46 or 39.7 per cent. had local recurrences following the closed plastic. This is a difference in the incidence of local recurrence following the two operative procedures of 9.6 per cent. or approximately 10 per cent. in favor of the Thiersch graft.

group of known dead in Tables XXXI, XXXII and Graph K were compared with the average post-operative longevity for those of the same group in which there was a local recurrence. This comparative analysis revealed a shortening of the average post-operative life in the event of a local recurrence, from 3.62 years' average without to 2.95 years with a recurrence.

TABLE XXXI.—*Average Length of Life for Groups of Different Age Incidence, of Patients Operated Upon for Carcinoma of the Breast. Patients Known to be Dead*

Age groups	Total no. of yrs. of life after oper.	No. of cases	Average length of life after oper. (yrs.)
20–24 years........	2.0	2	1
25–29 years........	15.5	7	2.21
30–34 years........	65.0	24	2.71
35–39 years........	110.5	47	2.35
40–44 years........	179.5	60	2.99
45–49 years........	274.0	68	4.03
50–54 years........	238.5	57	4.18
55–59 years........	146.0	44	3.32
60–64 years........	194.0	44	4.41
65–69 years........	134.5	27	4.98
70–74 years........	39.5	11	3.59
75–79 years........	23.0	2	11.50
Totals............	1422.0	393	3.62

Peculiarly enough this comes to 0.67 of a year, or about eight months, which is exactly the difference found in the post-operative longevity between the

TABLE XXXII.—*Average Length of Life, for Groups of Different Age Incidence, of Patients Operated Upon for Carcinoma of the Breast. Patients Known to be Dead*

Age groups	Total no. of yrs. of life after oper.	No. of cases	Average length of life after oper. (yrs.)
20–29 years........	17.5	9	1.95
30–39 years........	175.5	71	2.47
40–49 years........	453.5	128	3.54
50–59 years........	384.5	101	3.81
60–69 years........	328.5	71	4.63
70–79 years........	62.5	13	4.81
Totals............	1422.0	393	3.62

See Graph K.

two operative procedures for the entire group. If the difference in the average length of life for those with and without a local recurrence is computed for each decade of years in which they were operated upon rather

TABLE XXXIII.—*Local Recurrences of Carcinoma of the Breast (Patients Known to be Dead)*

Johns Hopkins Hospital (1889–1931)

Decades	No. of cases of recurrences	No. of cases	Per cent. of recurrences	Total length of life (yrs.) after local recurrences	Average length of life after local recurrences
1889.............		2	—	—	—
1890–1899.........	49	141	34.8	141.5	2.89 years
1900–1909.........	35	134	26.1	107.0	3.45 years
1910–1919.........	27	101	26.7	73.0	2.70 years
1920–1929.........	5	40	12.5	8.5	1.70 years
1930–1931.........	—	2	—	—	—
Totals............	116	420		330.0	2.95 years

Difference in the average length of life of patients with and without recurrence is 3.62 years minus 2.95, or 0.67 of a year. If, however, the earlier decades are used concerning which we have from a statistical standpoint more accurate data, there is a difference of 1.68 years in the longevity of those having and not having a recurrence. Compare Tables XXVIII and XXXIII.

than the decade in reference to their age, it is at once apparent that there is a difference of 1.68 years for the decade ending in 1899. In other words, those patients operated upon between 1889 and 1899 that developed a local

TABLE XXXIV.—*Frequency Distribution, According to Age (Ten-Year Grouping) of 116 Cases of Carcinoma of the Breast, Where There Was a Local Recurrence*
Johns Hopkins Hospital (1889–1931)

Age in yrs.	Cases of carcinoma of breast, age of incidence	Local recurrences, carcinoma of breast	Per cent. of cases having local recurrences
20–29	9	6	66.7
30–39	75	31	41.3
40–49	134	30	22.4
50–59	110	26	23.6
60–69	77	19	24.7
70–79	14	3	21.4
Unknown	1	1	—
Totals	420	116	

On the whole the younger the patient is the more susceptible to local recurrence.

TABLE XXXV.—*The Situation of Local Recurrences after Thiersch Graft and Closed Plastic Operations for Carcinoma of the Breast*
Johns Hopkins Hospital (1889–1931)

Thiersch graft			Closed plastic		
Site of local recurrences	No. of local recurrences	Per cent. of local recurrences	Site of local recurrences	No. of local recurrences	Per cent. of local recurrences
A	2	2.1	E	2	4.3
I	13	13.4	B	21	45.7
CDHI	1	1.0	BJ	5	10.9
CDH	53	54.6	J	2	4.3
ACDH	8	8.2	BGEF	1	2.2
C	3	3.1	GEF	1	2.2
CD	3	3.1	GEJ	1	2.2
DH	2	2.1	BG	5	10.9
			BE	1	2.2
			G	1	2.2
			GF	1	2.2
Unknown	12	12.4	Unknown	5	10.9
Total	97	100.0		46	100.2

In one case where there was a local recurrence, the data concerning the type of operation were not given, therefore there were 144 local recurrences.

See Bar Diagrams L and M. The great majority of local recurrences involve the skin; particularly is this true of the closed plastic. Therefore, more skin should be removed.

recurrence lived 1.68 years less than those patients in whom there were no local recurrences. This difference diminishes, as seen by a comparison of Tables XXVIII and XXXIII, in the later or more recent decades because there is a larger percentage of those with local recurrences that have died, for these patients die sooner after operation. This, together with the fact that more patients are still living in these decades and therefore their post-operative longevity cannot be determined, accounts for the shorter average length of life so far computed for the decade and a closer approach to the average length of life of those having a local recurrence. In future years when those whose post-operative life is destined to be long have been given a sufficient number of years to have completed their life, the average length of post-operative life of those not having a recurrence will as in the earlier years increase the average for that particular decade. The more recent the
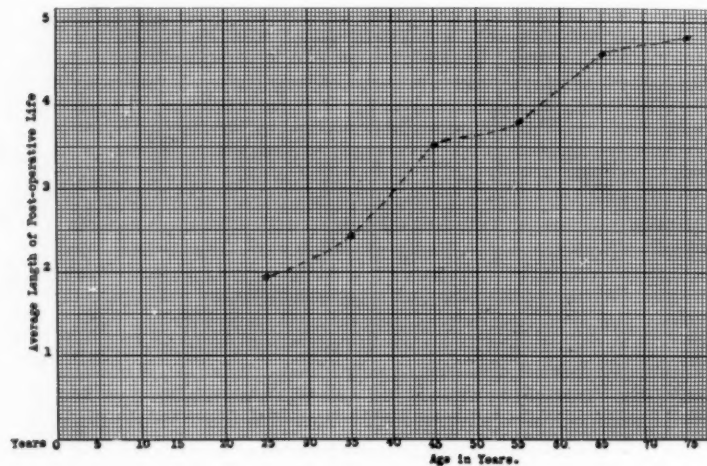
GRAPH K.—Age in years. Average length of life after operation of patients having carcinoma of the breast. (Patients known to be dead.)

decade the more closely the averages for those having or not having a local recurrence will approximate each other. The converse seems also to be true, *i.e.*, the earlier or more remote the decade the more divergent will be these averages.

The data as to the presence or absence of a local recurrence which can be seen by the patient, family, and attending physician are apt to be far more accurate than the information regarding metastases or other causes of death. At the same time, it is the best criterion of the efficacy of an operative procedure. If the disease has been cured locally the operator has fulfilled his responsibility.

The effect of age on the probability of a local recurrence is shown in Table XXXIV, which demonstrates the increased likelihood of a local recurrence in the younger patient, and *vice versa*.

Further evidence of the advisability of sacrificing the largest possible area of skin is supplied when the *location of the recurrences are considered.*

(Table XXXV, Bar Diagrams L and M.)   The large majority of the local recurrences following the closed plastic procedure occurred along the incision,

BAR DIAGRAM L

*The Situation of Local Recurrences after a Thiersch Graft Operation for Carcinoma of the Breast
Johns Hopkins Hospital (1889–1931)*
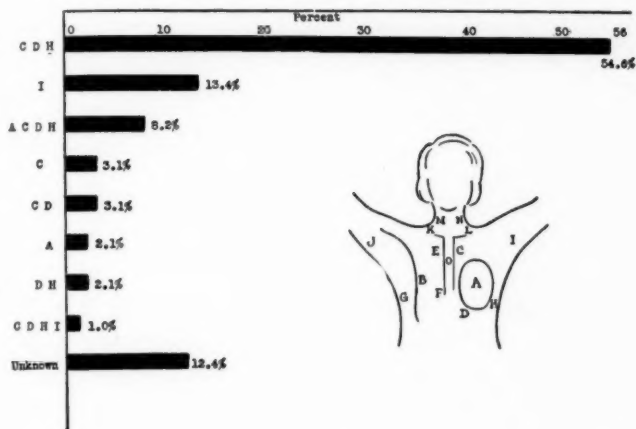
in the skin and subcutaneous tissue, where there was no evidence of carcinoma before operation.   However, whether these regional metastases in the skin and subcutaneous tissue, or extensions from the primary tumor were

BAR DIAGRAM M

*The Situation of Local Recurrences after a Closed Plastic Operation for Carcinoma of the Breast
Johns Hopkins Hospital (1889–1931)*
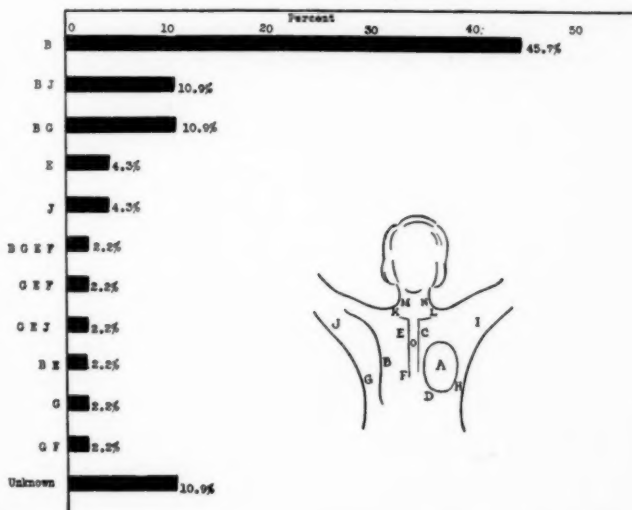
present before operation but clinically were unrecognized, or whether they were reinoculations at the time of operation it matters not, for the only manner in which they can be prevented is by avoiding the primary tumor by a wider margin and removing a greater amount of skin and subcutaneous

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tissue in the immediate environment. In the Thiersch graft operation there were also some tumors that recurred in the skin about the periphery of the grafted area, but the great majority seem to be deep beneath the skin, arising in the chest-wall and later involving the surface. These probably began either in the lymphatic vessels along the course of the anterior perforating branches of the internal mammary artery or in the slips of origin of the pectoralis major muscle. However, it is questionable whether local recurrences in these deep situations could be prevented by a more careful dissection coupled with some form of mild cauterization. Probably the incidence of local recurrence in the Thiersch graft group could have been reduced even more, had a greater amount of skin and subcutaneous tissue been removed. At least this seems probable in some cases of this group in which there were eventually local recurrences in the skin about the grafted area. For when the fact that the breast is an appendage of the skin is taken into consideration, is it not logical that the adjacent skin in the region of the primary tumor would be the most likely site of recurrence? Therefore, it would seem that the removal of a large area of skin is just as important, if not more so, as that of the subcutaneous tissue or underlying muscles. Certainly in this series by far the larger percentage of recurrences took place in the skin and subcutaneous tissue immediately underlying it. It would therefore appear to us to be paradoxical to make the incision close to the tumor in the skin and superficial subcutaneous tissue and excise widely the deep fascial layers and muscle beneath, but just as much so than the converse procedure. It is, of course, not practical to consider the removal of the skin commensurate with the wide excision of subcutaneous tissue and deeper structures, or, in other words, equal to the limits of the operative field. This would mean denuding the chest-wall. But it does seem that the larger the amount of skin removed the less the chance of local recurrence, the greater the probability of survival over the first perilous five years and a definite increase in post-operative longevity. Therefore, very large areas of skin should be removed regardless of the size or position of the tumor, whether deep in the breast or superficial, leaving the closure of the defect out of mind until the end of the operation. No matter how large the defect, it may be closed immediately by Thiersch or later by Reverdin grafts. In unusual cases it is occasionally possible to close without grafting, but the plastic incision should certainly be planned after the operation is finished and not in the beginning. The superiority of the results of the Thiersch graft group in this series of cases lies wholly in the wide excision of the skin. It is not probable that the presence of a graft is of any importance in the prevention of a recurrence. The operator, after removing more skin than he feels necessary with every point in the incision equidistant from the tumor, may, after completing the operation and obliterating the dead space in the axilla without tension, close as he can with the skin flaps that remain. The manner from the standpoint of curing the disease is inconsequential. If there is, and except in unusual cases there will be, a defect, it may be grafted, but it would appear to be the defect, not the

graft, that tends to prevent a local recurrence. The sloughing of the skin flaps, while rather unsurgical, following some plastic operations would appear to be a fortunate intervention for the patient. Therefore, if an operative procedure be selected on the basis of the lower percentage of local recurrences, the slight but definite increased post-operative longevity, and the fact that a greater percentage of patients will survive the first five years, then the preference for the Halsted Thiersch graft operation, or a procedure of this type in which a large amount of skin is exsected, is indisputable.

When the percentage of local recurrence was considered from the standpoint of the pathological variety of the tumor (Table XXXVI), it was found

TABLE XXXVI.—*Local Recurrences after Thiersch Graft and Closed Plastic Operations, for Carcinoma of the Breast, Classified as to Type of Tumor*

Johns Hopkins Hospital (1889–1931)

Type of tumor	Thiersch Graft			Closed Plastic		
	No. of operations	No. of local recurrences	Per cent. of local recurrences	No. of operations	No. of local recurrences	Per cent. of local recurrences
Scirrhous...........	217	72	33.2	79	29	36.7
Medullary..........	64	14	21.9	21	6	28.6
Adeno..............	28	6	21.4	7	4	57.1
Colloid.............	4	—	—	1	1	100.0
Cancer in cyst......	2	2	100.0	1	1	100.0
Comedo............	1	—	—	—	—	—
Paget's.............	1	—	—	—	—	—
Carcinoma.........	2	1	50.0	3	3	100.0
Spinal cell..........	1	—	—	—	—	—
Colloid adeno.......	1	—	—	—	—	—
Sarcoma...........	1	1	100.0	1	—	—
Intracystic papilloma.	1	1	100.0	—	—	—
Unknown..........	1	—	—	4	2	50.0
Totals.............	324	97		117	46	

Four hundred and forty-one cases comprising the group of known dead and living with a recurrence. See Bar Diagram N.

that the highest percentage occurred with scirrhous, with adeno-carcinoma, and medullary cancer, in the order named. When the type of tumor is considered in conjunction with the method of operation the results can be seen in Bar Diagram N. With each type of tumor the percentage of local recurrence is less with the Thiersch graft procedure.

In Table XXXVII an attempt has been made to establish a relation between the duration of the tumor before operation and the length of life afterward, in the group of patients known to have died. From this table the average length of life for several periods of disease duration was calculated and it was found that with a duration of three months the average length of

life was 3.87 years; for six months, 2.86 years; for nine months, 3.07 years; for one year, 2.57 years; for two years, 3.54 years; for three years, 3.65 years; for four years, 4.91 years. It would seem that although there is con-

BAR DIAGRAM N

The Percent of Local Recurrences after Thiersch Graft and Closed Plastic Operations Classified as to Type of Tumor
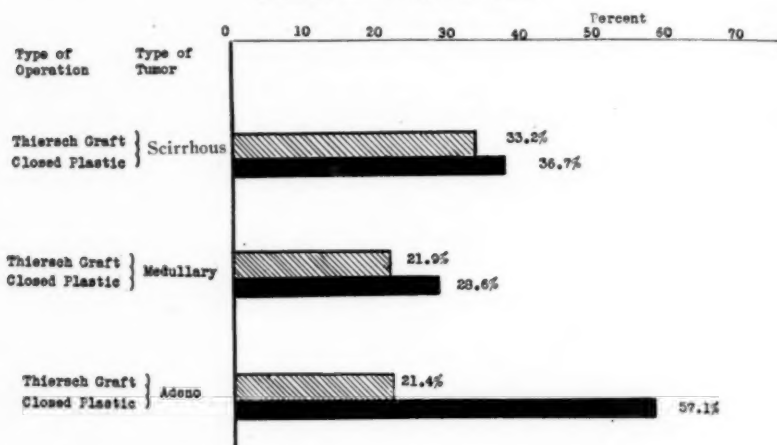
The black bars represent the results following the closed plastic procedure for the various types of tumors, whereas the light shadowed ones represent the results following the Thiersch.

siderable inconstancy in the comparison between pre-operative duration of the tumor and the post-operative length of life up to one year's duration, certainly after one year, the longer the duration of the tumor before operation the longer the life of the patient after the onset. This might be concluded
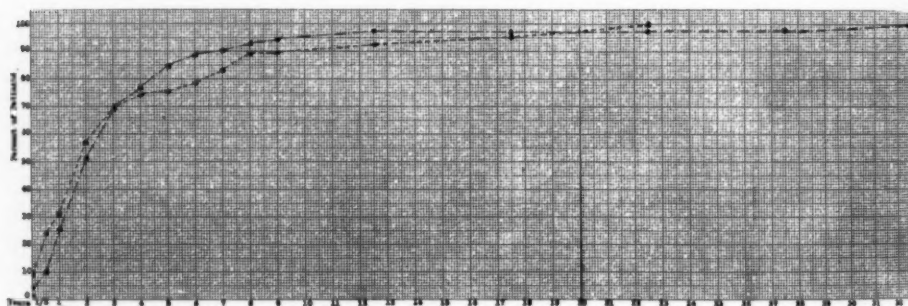
GRAPH O.—The percent of patients that had died by the end of each successive year; for the cases where the duration of the tumor before operation was three months or less and where it was more than one year, but not greater than two years. Three months _ _ _ _ _ _. Two years _._._._._. * In hospital.

from the average length of post-operative life for groups in which the tumors were of varying pre-operative duration. This is probably due in a large measure to the fact that slow-growing tumors are of longer duration so far as the patient's knowledge goes. This is only apparent. When, however, one studies Table XXXVII, it will be noted that there are two out-

TABLE XXXVII.—*Four Hundred and Twenty Cases of Carcinoma of the Breast. Patients Known Dead. Duration of Carcinoma Prior to Operation*

Time (Length of life after operation)	Unknown	3 mos.	6 mos.	9 mos.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5–9 yrs.	10–19 yrs.	20–29 yrs.	30 yrs. and over	Total
Unknown	1	4	4	3	3	6	4	1	1				27
In hospital	1	6	5	3	3	3	2	1	1				25
6 months		10	4	11	8	5	1	3	1	1			44
1st year		5	11	8	15	11	2	3	1	1	1		58
2nd year		17	23	10	15	19	6	1	4	2	1		98
3rd year		8	5	3	6	13	1	2	1	1	2	2	44
4th year	2	3	6	6	6	6	3		3		1	1	37
5th year		3	6		2	3	1		1				16
6th year		1	3	1	3	6		1	1				16
7th year		2	3		3	3	1			1			13
8th year		3	1		1	2		1	1				9
9th year		4											4
10th–14th year		2		2	2	3	1	1	1	1			13
15th–19th year		2		1	1		1						5
20th–24th year				5	1		1	1					8
25th–29th year										1			1
30th–34th year								2					2
Totals	4	70	71	53	69	80	24	17	16	8	5	3	420
Total No. of years		271	203	162.5	177	283.5	87.5	83.5					
Average length of post-oper. life, years		3.87	2.86	3.07	2.57	3.54	3.65	4.91					

With a duration of three months the average length of life is 3.87 years. Six months, 2.86 years; nine months, 3.07 years; one year, 2.57 years; two years, 3.54 years; *etc*. There are two main groups, however, one in which the duration of the growth was three months or less and that group in which the duration was between one and two years but no more than two. The group of three months or less comprised sixty-six patients and the two-year one seventy-four cases. This portion of Table XXXVII was then placed in cumulative form in Table XXXVIII.

standing groups of approximately the same size but of marked divergence as to the duration of the tumor before operation, *i.e.*, the group in which the duration of the growth was three months or less and two years, the latter group including all cases of more than one, but no more than two years' duration. The group of three months' duration comprised sixty-six patients and the two-year group seventy-four cases. This portion of Table XXXVII

TABLE XXXVIII.—*The Per Cent. of Patients That Had Died by the End of Each Successive Year; for the Cases Where the Duration of the Tumor before Operation was Three Months or Less, and Where It Was More than One Year but Was Not Greater than Two Years*

Johns Hopkins Hospital (1889–1931)

Length of post-oper. life	Duration of tumor before oper.	
	3 mos. Per cent. of patients	1–2 yrs. Per cent. of patients
In hospital	9.1	4.1
6 months or less	24.2	10.8
1 year or less	31.8	25.7
2 years or less	57.6	51.4
3 years or less	69.7	68.9
4 years or less	74.2	77.0
5 years or less	75.8	85.1
6 years or less	78.8	89.2
7 years or less	83.3	90.5
8 years or less	89.4	93.2
9 years or less	89.4	94.6
10–14 years or less	92.4	97.3
15–19 years or less	95.5	97.3
20–24 years or less	100.0	97.3
25–29 years or less	—	97.3
30–34 years or less	—	100.0

Graph O. This table and curve demonstrate that of those patients coming into the hospital within three months of discovery of the tumor a greater percentage die in each successive year up to the third year than of those of the two-year duration group. After three years, however, a complete reversal occurs and a smaller percentage of the three months' group die each succeeding year than the two-year group, indicating that in spite of the most radical operation in some of the patients comprising the three months' group there had occurred already metastases beyond the limits of the operative field. On the average, however, it shows that the earlier the case is presented for surgical therapy the more likelihood of the disease being a localized one.

was then placed in cumulative form (Table XXXVIII), and the results plotted in Graph O. This table and curve demonstrate that of those patients coming into the hospital within three months of the discovery of the tumor a greater percentage die in each successive year up to the third year than of those of the two-year duration group. After three years, however, a complete reversal occurs and a smaller percentage of the three-months group dies each succeeding year than of the two-year group. This would indicate that

TABLE XXXIX.—*Ninety-seven Cases of Carcinoma of the Breast; Patients Reported Well. Duration of Carcinoma of the Breast Prior to Operation*

Length of life after operation	Unknown	3 mos.	6 mos.	9 mos.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6–10 yrs.	40 yrs.	Total
Unknown.		2	1		1							5*
In hospital.		4	1		2							7*
6 months.		1	1	1	1							4
1 year.		1	1		1							3
2 years.		3	3	2	2	2		1				13*
3 years.		4	1	2	2	1	1		1			12*
4 years.		7	1		2	3						
5 years.			1			1		1				
6 years.		1	4	1	1		1	2		1		9*
7 years.		2			1							
8 years.		1	1		1					1		
9 years.		1	3	2	1		1	2		1		
10–14 years.		2	3	1	1	1	1	1	1	1		12
15–19 years.		6	1	1	1	1	1	1	1			12
20–24 years.			1	1	1	1		1	1	1		5
25–29 years.					1	1					1	4
Total.	2	29	22	7	11	9	3	7	3	3	1	97

Totals for the years* are larger because the operations were performed in recent years.

In Table XXXIX the relation of the duration of the tumor before operation and the longevity for the group of patients now living was estimated and there is a lack of definite tendency, but one striking feature is that over one-half of those now living were operated upon within six months of the onset. It is impossible in this group to work the average length of life because they are still living.

although a radical operation was performed very early in the duration of the disease in that group of patients comprising the three-months group a certain percentage, owing to the type of tumor and rapidity of growth, had already metastasized beyond the limits of operability. In the remainder of this group the carcinoma was yet confined within operative limits and these patients surviving the three-year period lived longer. The converse may be said concerning members of the group in which the duration of the lesion was two years and who did not die as rapidly as those of the other group and indicates the relative slow growth of the tumor. After the three-year period the death rate in this group is higher per year, a fact which appeared to be due to extension of the carcinoma to other parts. The duration, therefore, is important from the standpoint of prognosis, because undoubtedly the post-operative longevity of the two-year group could have been increased if they had submitted to a radical operation earlier in the course of the disease. On the other hand, in spite of the early treatment in the three-months or less group a large percentage die with metastases within three years. Thus the type of tumor from a histological as well as a biological standpoint plays in our present state of knowledge an indeterminable rôle.

In Table XXXIX the relation of *the duration of the tumor before operation and the longevity for the group of patients now living* was estimated and there was found to be a lack of definite tendency, but one striking feature is that over one-half of those now living were operated upon within six months of onset. It is impossible in this group to establish the average length of life because they are still living.

A study of the length of life after operation in connection with the type of tumor was made of the 420 patients known to be dead. This computation is tabulated in Table XL. It is to be noted that of the three main types of carcinoma of the breast encountered in the study, *i.e.*, scirrhous, medullary and adeno-carcinoma, the post-operative length of life of the patients suffering from medullary carcinoma was on the whole shorter than that of the patients having scirrhous or adeno-carcinoma. The latter, on the average, while fewer in number, lived longer than either of the former. This table gives the absolute number of patients who died each successive year together with the percentage of the whole of each separate group. Table XLI shows the material of Table XL in cumulative form, and demonstrates the same points referred to under Table XL. The calculations for the first ten years are the most interesting because following this period the remaining cases are few and scattered, and by this time 90 per cent. of the patients have died. At the end of two years 53.9 per cent. of scirrhous, 59.3 per cent. of medullary, and only 21.9 per cent. of adeno-carcinoma patients were dead. By the end of five years about three-fourths of the scirrhous and medullary but only three-fifths of the adeno-carcinoma patients were dead. The isolated cases of other and various types of carcinomata, shown in Table XL, were considered too few to include in Table XLI.

TABLE XL.—*Carcinoma of the Breast. Length of Post-Operative Life with Type of Tumor, 420 Cases*

Length of life	Scirrhous No.	Per cent.	Medullary No.	Per cent.	Adeno No.	Per cent.	Simple carc.	Sar-coma	Paget's Cancer in cyst	Col-loid	Spinal cell adeno	Col-loid medo	Co-	X
In hospital	9	3.2	7	8.6	2	6.3				1				1
6 months	36	12.7	6	7.4										
1 year	39	13.7	18	22.2	3	9.4	2							
2 years	69	24.3	17	21.0	2	6.3	3							2
3 years	28	9.9	9	11.1	8	25.0								
4 years	28	9.9	5	6.2	2	6.3		1						
5 years	13	4.6	1	1.2	2	6.3			1					2
6 years	13	4.6	6	7.4	1	3.1				1	1			
7 years	12	4.2			3	9.4			1	1	1			
8 years	6	2.1	3	3.7	1	3.1								
9 years	2	.7	1	1.2										
10 years	4	1.4	2	2.5	1	3.1								
11 years	2	.7	1	1.2							1			
12 years	2	.7			1	3.1								
13 years	1	.4			1	3.1					1			
14 years												1		1
15 years	1	.4	2	2.5	1	3.1								
16 years			1	1.2										
17 years														
18 years														
19 years														1
20 years					1	3.1								
21 years	2	.7												
22 years	1	.4												
23 years	2	.7											1	
24 years	1	.4			1	3.1								
25 years	1	.4			1	3.1								
28 years														
32 years	1	.4	1	1.2										
X	11	3.9	1	1.2	2	6.3								
Totals	284	100.8	81	99.8	32	100.1	6	1	1	3	4	1	1	5	420

It is to be noted that the post-operative length of life of those patients affected with medullary carcinoma was on the whole shorter than that of the patients having scirrhous or adeno-carcinoma. The latter lived longer than either of the former. This table gives the absolute number of cases having died each successive year together with the percentage of the whole of each separate group.

TABLE XLI.—*Length of Life after Operation for Carcinoma of the Breast with Type of Tumor. Four Hundred and Twenty Cases Known Dead. Cumulative*

Johns Hopkins Hospital (1889–1931)

Length of life	Scirrhous		Medullary		Adeno	
	No. of cases	Per cent. cases	No. of cases	Per cent. cases	No. of cases	Per cent. cases
In hospital	9	3.2	7	8.6	2	6.3
6 months or less	45	15.8	13	16.0	2	6.3
1 year or less	84	29.6	31	38.3	5	15.6
2 years or less	153	53.9	48	59.3	7	21.9
3 years or less	181	63.7	57	70.4	15	46.9
4 years or less	209	73.6	62	76.5	17	53.1
5 years or less	222	78.2	63	77.8	19	59.4
6 years or less	235	82.7	69	85.2	20	62.5
7 years or less	247	87.0	72	88.9	23	71.9
8 years or less	253	89.1	72	88.9	24	75.0
9 years or less	255	89.8	73	90.1	25	78.1
10 years or less	259	91.2	75	92.6	25	78.1
11 years or less	261	91.9	76	93.8	25	78.1
12 years or less	263	92.6	78	96.3	25	78.1
13 years or less	264	93.0	78	96.3	26	81.3
14 years or less	264	93.0	78	96.3	27	84.4
15 years or less	265	93.3	78	96.3	27	84.4
16 years or less	266	93.7	79	97.5	28	87.5
17 years or less	—	—	—	—	—	—
19 years or less	266	93.7	80	98.8	28	87.5
20 years or less	266	93.7	80	98.8	29	90.6
21 years or less	268	94.0	80	98.8	29	90.6
22 years or less	270	95.1	80	98.8	29	90.6
23 years or less	271	95.4	80	98.8	29	90.6
24 years or less	272	95.8	80	98.8	29	90.6
25 years or less	272	95.8	80	98.8	29	90.6
28 years or less	273	96.1	80	98.8	30	93.8
32 years or less	273	96.1	80	98.8	30	93.8
Unknown	11	3.9	1	1.2	2	6.3
Totals	284	100.0	81	100.0	32	100.1

Shows the material of Table XL in cumulative form. The calculations for the first ten years are most interesting because following this period the remaining cases are few and scattered and by this time 90 per cent. of the cases have died. At the end of two years 53.9 per cent. of scirrhous, 59.3 per cent. of medullary, and only 21.9 per cent. of adeno-carcinoma were dead. By the end of five years about three-fourths of scirrhous and medullary, but only three-fifths of adeno-carcinoma were dead. The few isolated cases of other and various types of carcinomata, shown in Table XL, were considered too few to include in Table XLI.

CANCER OF THE BREAST

The average length of life following operation for carcinoma of the breast for patients known to be dead was computed with reference to the age of the

TABLE XLII.—*Complete Expectation of Life in Years, 1919–1920, for White Females*

Exact age in yrs.	E_x^0
0	57.52
1	60.63
2	60.60
7	57.05
12	52.62
17	48.22
22	44.21
27	40.46
32	36.77
37	32.99
42	29.11
47	25.21
52	21.43
57	17.84
62	14.50
67	11.49
72	8.92
77	6.77
82	5.08
87	3.76
92	2.62

From U. S. Abridged Life Table, 1919–1920 (pp. 26–27).

In Aggregate—New England States, New York, New Jersey, Pennsylvania, Maryland, District of Columbia, Virginia, North Carolina, South Carolina, Tennessee, Kentucky, Ohio, Indiana, Illinois, Michigan, Wisconsin, Minnesota, Missouri, Kansas, Utah, California, Oregon, Washington.

The average length of life following operation for carcinoma of the breast for patients known to be dead was computed with reference to the age of the patient at the time of operation. This computation is shown in Table XXXI wherein the average post-operative length of life is charted in five-year groups. In a distribution of normal individuals the life expectancy would be greatest for the group from twenty to twenty-four and diminishes for each successive year as shown in this Table XLII, Graph P, whereas in the group of individuals affected with carcinoma the average length of life is least in the earlier pentades, Table XXXI, beginning with twenty to twenty-four years and increased successively, except the periods thirty-five to thirty-nine and fifty-five to fifty-nine, until the seventieth year. The decline following this period of life might readily be explained by the diseases of old age. An inexplicable drop occurs for the age group fifty-five to fifty-nine. The average post-operative length of life increases in the cases affected with carcinoma with the advance in the age of incidence. Graphically demonstrated in Graph K. This shows conclusively that the older the patients at the time of operation the greater the life expectancy following operation.

patient at the time of operation. This computation is shown in Table XXXI wherein the average post-operative length of life is charted in five-year groups.

In a distribution of normal individuals the life expectancy would be great-

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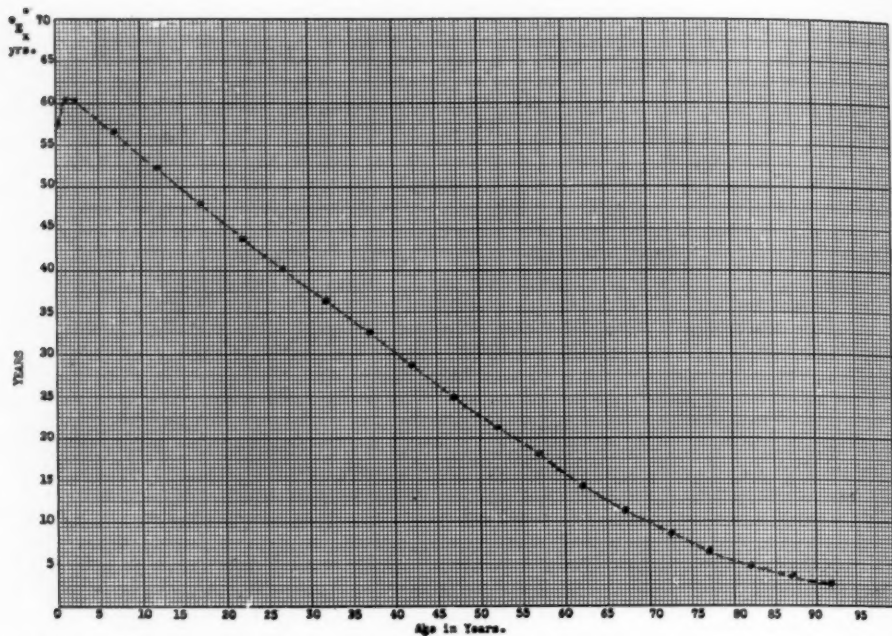
GRAPH P.—Age in years. Showing the complete expectation of life in years, 1919-1920, for white females. $^{o}E_{x}$—Expectation of life.

est for the group from twenty to twenty-four and diminishes for each successive year as shown in Table XLII and Graph P, whereas in the group of individuals affected with carcinoma the average length of life was least in the
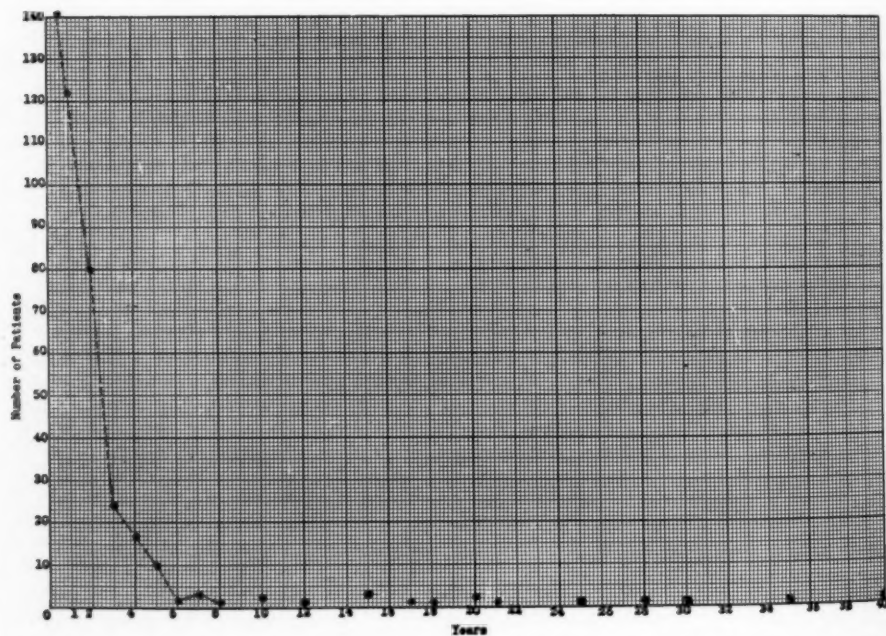
GRAPH Q.—Duration of carcinoma of breast from onset of disease to operation, 416 cases (dead).

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earlier pentades (Table XXXI), beginning with twenty to twenty-four years, and increased successively, excepting the periods thirty-five to thirty-nine, and fifty-five to fifty-nine, until the seventieth year. The decline following this period of life might readily be explained by the diseases of old age. An inexplicable drop in the average length of life occurs for the age group fifty-five to fifty-nine. In Table XXXII is shown the average length of life of

TABLE XLIII.—*The Duration of the Tumor from Onset to Operation for 420 Patients Having Carcinoma of the Breast*

Johns Hopkins Hospital (1889–1931)

Time duration from onset to operation	Absolute no. of cases	Per cent. of cases	Cumulative no. of cases	Per cent. of cumulative cases
6 months........................	141	33.6	141	33.6
1 year..........................	122	29.0	263	62.6
2 years.........................	80	19.0	343	81.7
3 years.........................	24	5.7	367	87.4
4 years.........................	17	4.0	384	91.4
5 years.........................	10	2.4	394	93.8
6 years.........................	2	.5	396	94.3
7 years.........................	3	.7	399	95.0
8 years.........................	1	.2	400	95.2
9 years.........................	—	—	—	—
10–14 years....................	3	.7	403	96.0
15–19 years....................	5	1.2	408	97.1
20–24 years....................	3	.7	411	97.9
25–29 years....................	2	.5	413	98.3
30–34 years....................	1	.2	414	98.6
35–39 years....................	1	.2	415	98.8
40–44 years....................	1	.2	416	99.0
Unknown........................	4	1.0	4	1.0
Totals.........................	420		420	100.0

Four cases of the group of 420 known dead could not be used because the histories were incomplete. See Graph Q. This table gives the absolute number of cases for six months and then the yearly periods after that, as well as the percentages of these respective periods. Also, the cumulative number of cases with their percentage is shown. It is to be noted that 33.6 per cent. of the patients had come in for examination within six months of the discovery of the tumor and 62.6 per cent. within the first year. More than four-fifths or 81.7 per cent. of these cases had consulted this hospital by the second year.

patients operated upon, the age of incidence being given in ten-year groups instead of five. This table demonstrates, as does Table XXXI, but without the minor fluctuations, that the average post-operative length of life increases with the advance in the age of incidence. This is demonstrated in Graph K and shows conclusively that the older the patient at the time of operation the greater the life expectancy following operation.

The duration of the disease from the time the patient first recognized the affection until operation was performed has been computed for the known dead, *i.e.*, for 420 cases with the exception of four in which the history was incomplete. This computation is shown in Table XLIII and Graph Q. This table gives the absolute number of cases for six months and then the yearly

TABLE XLIV.—*The Absolute Number of Patients for Various Durations of Life from the Onset of Carcinoma of the Breast until Death (392 Patients Known Dead)**

Johns Hopkins Hospital (1889–1931)

Duration of life from onset of disease until death	Absolute no. of cases	Per cent. of cases	Cumula-tive	Per cent. dead	Per cent. alive
6 months or less............	11	2.8	11	2.8	97.2
1 year....................	45	11.5	56	14.3	85.7
2 years...................	70	17.9	126	32.1	67.9
3 years...................	68	17.3	194	49.5	50.5
4 years...................	39	9.9	233	59.4	40.6
5 years...................	38	9.7	271	69.1	30.9
6 years...................	18	4.6	289	73.7	26.3
7 years...................	28	7.1	317	80.9	19.1
8 years...................	11	2.8	328	83.7	16.3
9 years...................	10	2.6	338	86.2	13.8
10–14 years..............	20	5.1	358	91.3	8.7
15–19 years..............	14	3.6	372	94.9	5.1
20–24 years..............	8	2.3	380	96.9	3.1
25–29 years..............	6	1.5	386	98.5	1.5
30–34 years..............	4	1.0	390	99.5	.5
35–39 years..............	1	.3	391	99.7	.3
40–44 years..............	1	.3	392	100.0	.0
Totals....................	392	100.0	392	100.0	.0

* In 28 cases there was insufficient data.

See Graph R. The actual number of cases which succumbed in various periods together with their percentage. Eleven or 2.8 per cent. died within six months and forty-five or 11.5 per cent. within six months and the first year. The cumulative column, however, shows the total number of cases dealt with in which the length of life is known, 392, and of these eleven died within the first six months. Therefore 381, or 97.2 per cent. lived more than six months, *etc.* It will be noted that the greater number of deaths occurred in the first, second, and third years. The cumulative column demonstrates the number of people alive for the successive years, which is objectively shown in Graph S.

periods after that, as well as the percentages of these respective periods. Also, the cumulative number of cases with their percentage is shown. It is to be noted that 33.6 per cent. of the patients had come in for examination within six months of the discovery of the tumor and 62.6 per cent. within the first year. More than four-fifths of all these patients (81.7 per cent.) had consulted this hospital by the second year. This tendency is shown in Graph G. (The points on the graph which are not joined by the curve represent isolated

Percent of Patients

Years

Duration Years

Absolute No. of Patients
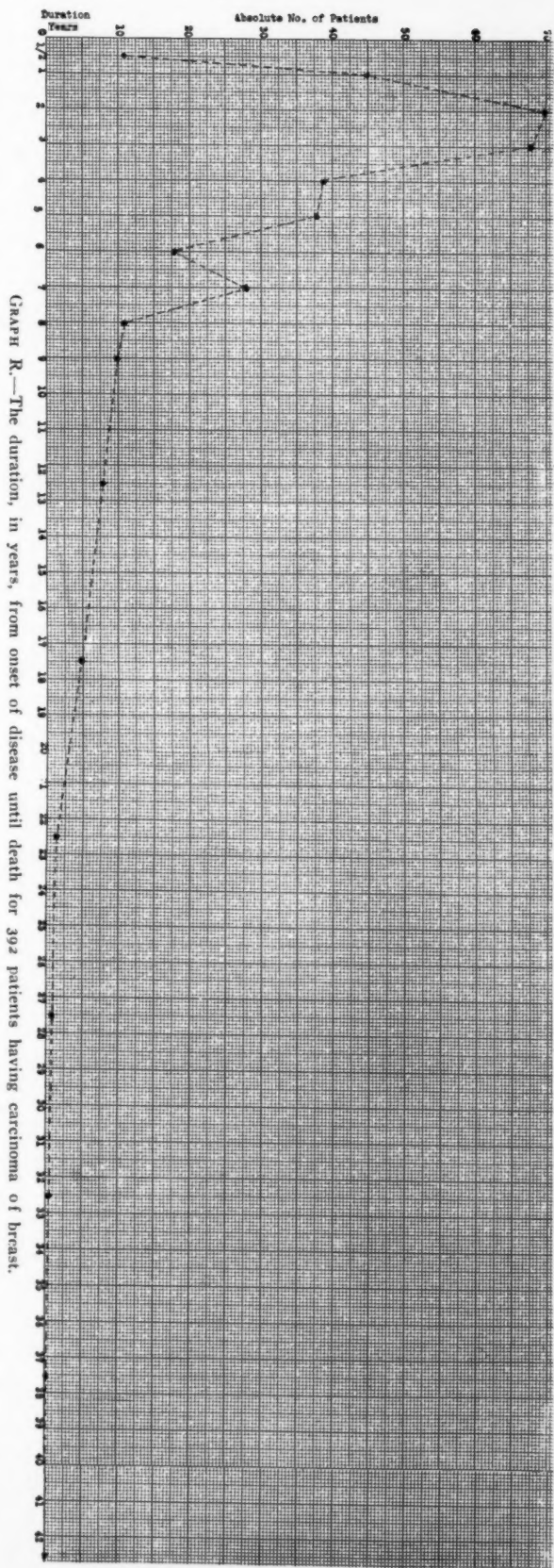
Graph R.—The duration, in years, from onset of disease until death for 392 patients having carcinoma of breast.
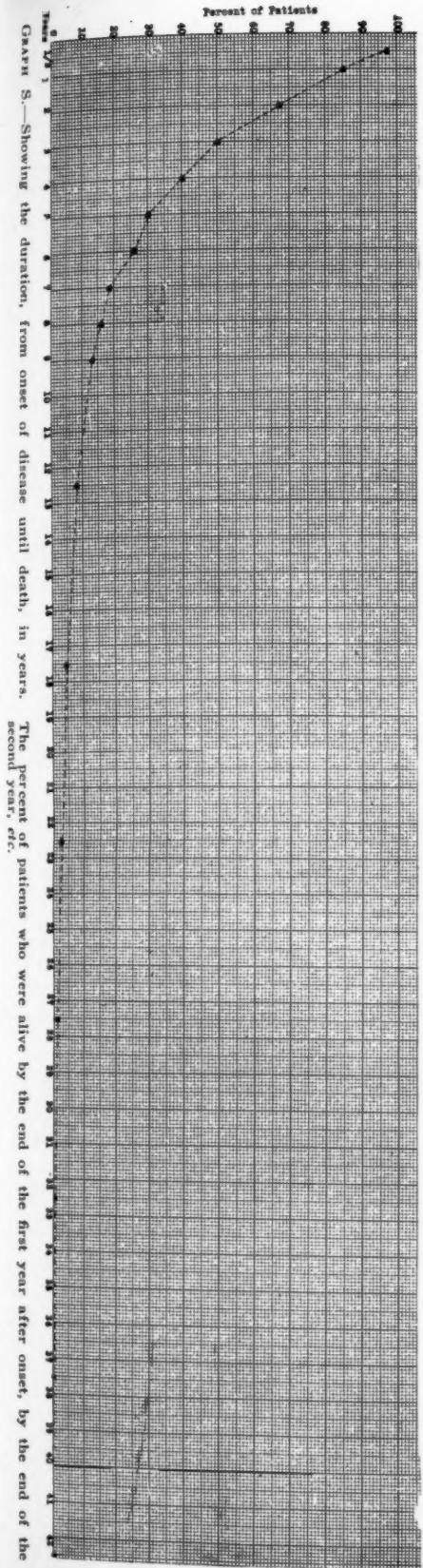
Graph S.—Showing the duration, from onset of disease until death, in years. The percent of patients who were alive by the end of the first year after onset, by the end of the second year, etc.

instances in which the duration from a charting standpoint was disconnected from the preceding period.)

In Table XLIV an analysis has been made of the duration of life in 420 cases of known dead from the time the patient first noticed the disease until death after operation. It has been necessary to exclude from this group twenty-eight cases because one factor has been unknown; thus 392 remained. In Table XLIV and Graph R the actual number of patients who succumbed in the various periods is shown together with their percentage. In this chart it will be noted that eleven patients (2.8 per cent.) died within six months, and forty-five (11.5 per cent.) within six months and the first year. The cumulative column, however, shows the total number of cases dealt with in

TABLE XLV.—*The Age Distribution and Per Cent. of Patients, Operated Upon for Carcinoma of the Breast, Who Lived Ten Years or More*

Johns Hopkins Hospital (1889–1931)

Age in yrs.	No. of patients	No. of patients who lived 10 yrs. or more	Per cent. of patients who lived 10 yrs. or more
30–39 years	109	13	11.9
40–49 years	192	20	10.4
50–59 years	159	21	13.2
60–69 years	94	12	12.7
70–79 years	19	5	26.3
Totals	573	71	12.2

Total number of possible cases 573, which number included the known dead and all cases living operated on prior to 1921 with the exception of those concerning whom there was no knowledge as to the length of life after operation. Seventy-one or 12.2 per cent. of these cases lived ten years or more. The percentage of patients living ten years or more for each age group with the exception of seventy to seventy-nine was practically the same, varying from 10.4 per cent. to 13.2 per cent.

which the length of life is known, 392, and of these eleven died within the first six months. Therefore, 381 (97.2 per cent.) lived more than six months, *etc.* It will be seen that the greater number of deaths occurred in the first, second and third year. The cumulative column demonstrates the number of people alive in the successive years which is objectively shown in Graph S.

A study has been made of the age distribution and percentage of patients operated upon for carcinoma of the breast who survived ten years or more.— (Table XLV.) The total number of possible cases was 573, this number including the known dead and all patients living that were operated on prior to 1921 with the exception of those concerning whom there was no knowledge as to the length of life after operation. Of these patients seventy-one (12.2 per cent.) lived ten years or more. The percentage of patients living ten years or more for each age group, with the exception of seventy to seventy-

nine, is practically the same, varying from 10.4 to 13.2 per cent. The average length of life for these individuals living ten years or more after having been operated on for carcinoma of the breast was calculated (Table XLVI) for the various age decades and it was found to be practically the same, 14.6 to 18.9 years, regardless of the decade. However, when these averages are compared with the normal life expectancy, it is at once apparent that there is a progressive decrease in the latter for each decade from thirty to seventy years of age, whereas the average length of life for the patients living ten years or more for each successive age decade more closely approximates the normal life expectancy for that period up to age sixty, when the average

TABLE XLVI.—*A Comparison of the Normal Expectancy of Life with the Average Post-operative Length of Life of Patients (Having Carcinoma of the Breast) Who Lived Ten Years or More*

Age in years	Normal expectancy in years	Average post-oper. life of pts. who lived more than ten years
30–39 years	34.88	16.6
40–49 years	27.16	18.9
50–59 years	19.63	16.5
60–69 years	12.99	15.5
70–79 years	7.85	14.6

Shows the average length of life for these individuals living ten years or more after operation. Calculated for the various age decades and is practically the same. When these averages are compared with the normal life expectancy it is at once apparent that there is a progressive decrease in the latter for each decade from thirty to seventy years of age. Whereas, the average length of life for the patients living ten years or more for each successive age decade more closely approximates the normal life expectancy for that period up to age sixty when the average length of life for this group was greater than normal. See Graph T. Those operated on after sixty and living more than ten years will have lived out their normal life. The later the age decade when they are operated upon the greater chance they have of completing their normal span of life, providing they live ten years.

length of life for this group was greater than normal. (Graph T.) All those from sixty on that have lived ten years or more will have lived out their normal life. The later the age decade in which they are operated upon the greater chance they have of living out their normal span of life, providing they live ten years. Of this group of seventy-one patients who lived more than ten years, forty-two (59.2 per cent.) were operated upon within one year of the discovery of the tumor. In twenty-seven (38.1 per cent.) the duration of the disease prior to operation was longer than one year. In two the duration was unknown. Apparently, in this group of patients who lived over ten years, an early diagnosis and operation were beneficial. Although bearing no relation to the above-mentioned forty-two cases there were also forty-two, or 59.2 per cent., of the seventy-one patients living more than ten years who had no regional metastases at the time of operation, although twenty-seven (38.1

per cent.) did have axillary regional metastases. These figures go to show that even in the presence of metastases the outlook is not entirely hopeless.

In fact, unless remote metastases can be demonstrated in the lungs, liver, bony skeleton or entirely outside the field of operation, one is not justified, according to our judgment, in pronouncing a patient inoperable. This opinion is based on the review of the hospital histories, which, together with the follow-up study, prove that in many cases there was a large breast tumor which had even ulcerated through the skin, with metastases to the axilla and even to the neck of the same side, and yet the patients were cured of *clinical* cancer by operation. We quote one case which illustrates the futility of attempting to give a prognosis from the clinical examination as well as the histological section. This patient, Surgical No. 18058 was operated upon by Doctor Sowers in 1905 at the age of sixty-six. She had a large tumor of long
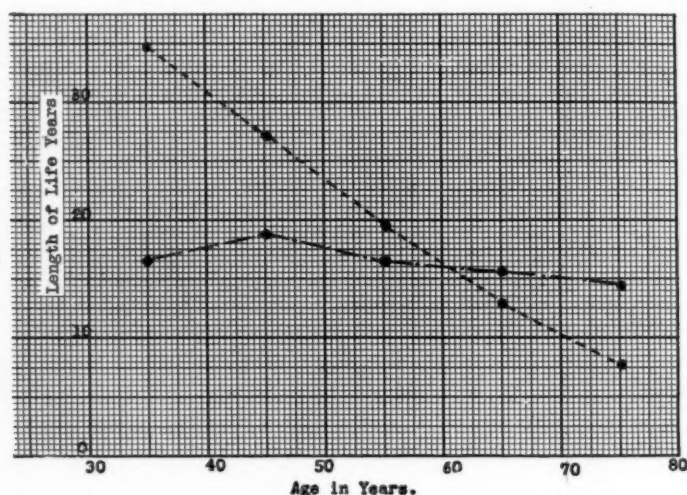
GRAPH T.—Age in years. A comparison of the normal life expectancy with the average post-operative life of patients, having carcinoma of the breast who lived ten years or more. Normal life expectancy _ _ _ _ _ _. Average post-operative life _ . _ . _ . _ . .

duration of her left breast, which had ulcerated through the overlying skin. There were regional metastases to the left axilla and neck. A radical Halsted Thiersch graft operation was performed, requiring over four hours for the completion of the operation. Not only was a very large area of skin removed, but the chest-wall, left axilla and left supraclavicular regions were meticulously denuded of all tissue. The patient had an uneventful convalescence and in June, 1931, was living and well at the age of ninety-three. Examination of the specimen removed showed the tumor to be a large infiltrating scirrhous carcinoma which invaded not only the overlying skin and subcutaneous tissue but also the underlying pectoral fascia and muscle. The operator and pathologist considered the prognosis at that time as poor. This, we think, is an example of what can be accomplished by allowing a large margin about the tumor and sacrificing a sufficient amount of skin combined with a most careful

radical procedure associated with patience and enthusiasm. Who can say that the disease has spread beyond *possible* operative limits, and deem it not necessary to make the greatest surgical effort? The only worthwhile modification of the Thiersch graft operation is to make it more, not less radical. It would seem far better to err on the radical side and take as much time at operation as is necessary rather than perform a rapid excision of the breast and not be radical enough. This one case of Sowers', which is almost one in

TABLE XLVII.—*Classification of 789 Cases of Carcinoma of the Breast as to Type of Tumor and as to the Presence or Absence of Metastases*

Johns Hopkins Hospital (1889–1931)

Type of tumor	With metastases		Without metastases		No data regarding metastases		Total No. of cases
	No. of cases	Per cent.	No. of cases	Per cent.	No. of cases	Per cent.	
Scirrhous	365	79.2	89	19.3	7	1.5	461
Adeno	46	68.7	20	29.9	1	1.5	67
Medullary	155	76.4	47	23.2	1	.5	203
Simple carc.	9	100.0	—	—	—	—	9
Sarcoma	1	33.3	2	66.7	—	—	3
Papillary	—	—	1	100.0	—	—	1
Colloid	5	41.6	7	58.3	—	—	12
Paget's	4	66.7	2	33.3	—	—	6
Comedo	1	100.0	—	—	—	—	1
Cancer in cyst	7	77.7	2	22.2	—	—	9
Colloid adeno	1	100.0	—	—	—	—	1
Intracystic papilloma	—	—	1	100.0	—	—	1
Unknown	6	40.0	1	6.7	8	53.2	15
Totals	600		172		17		789

Six hundred patients had metastases while in 172 their presence could not be demonstrated. It will be seen that 454 were affected with scirrhous and that of this number 365 or 79.2 per cent. had metastases and 89 or 19.3 per cent. were without them. The percentage for the medullary type was practically the same. Out of 202 cases, 155 or 76.4 per cent., had metastases; 47 or 23.2 per cent. had none. Of the groups classified microscopically as adenocarcinoma, which contained sixty-six cases, forty-six or 68.7 per cent. had metastases, while twenty or 29.9 per cent. had none.

a thousand, justifies the most radical surgical treatment in cases of extensive involvement even though the prognosis is apparently hopeless, as long as the disease has remained within possible operative limits.

An analysis was made of 772 cases in regard to the relation of metastases to the type of neoplasm present. Table XLVII reveals that in 600 patients metastases occurred, whereas in 172 cases none were detected. Of the patients suffering from scirrhous carcinoma, 79.2 per cent. had metastases and also

76.4 per cent. of those with medullary cancer. Only 29.9 per cent. of those with adeno-carcinoma had metastases.

It has been possible to analyze the cause of death in the 420 cases comprising the known dead group (Table L). It is to be noted that of this group 206 patients (49 per cent.) were known to have died of carcinoma. In sixty-one (14.5 per cent.) the causes of death were given as due to other conditions, which, when one takes into consideration that many of these follow-up letters were answered not always by general practitioners but also by members of the family, the accuracy of some of the diagnoses is questionable. If only those cases in which it was almost certain the patient died, at least with car-

TABLE XLVIII.—*The Growth of the Tumor, According to Age, for 415 Cases of Carcinoma of the Breast. These Patients Are Known to be Dead*

Johns Hopkins Hospital (1889–1931)

Years Age	Rate of growth		
	Slow	Rapid	Slow to rapid
	Per cent. of cases	Per cent. of cases	Per cent. of cases
20–29 years	11.1	44.4	—
30–39 years	26.7	16.0	8.0
40–49 years	32.3	13.5	12.0
50–59 years	28.4	14.7	13.8
60–69 years	25.3	10.7	6.7
70–79 years	28.6	7.1	14.3

The percentage of rapid growth was much larger for the twenty to twenty-nine age group than for any of the succeeding ones. In the age decade seventy to seventy-nine, 28.6 per cent. of the cases had slow-growing tumors. It would seem that under thirty years of age the larger percentage of patients had rapid-growing tumors and over seventy there is a larger percentage of slow-growing tumors. In the ages thirty to sixty-nine there appeared to be very little difference in the rate of growth.

cinoma if not of it, are removed from this group of sixty-one, there are seventeen cases or 4 per cent. in which the cause of death was probably not carcinoma.

The group of patients concerning whom no information could be obtained numbered 153 (36.4 per cent.). Thus, of 49 per cent. or 206 cases of the 420 known dead group we have unquestionable information that the cause of death was carcinoma. It is highly probable that of the sixty-one cases or 14.5 per cent. who were supposed to have died of other causes, at least forty-four or 10.5 per cent. died of carcinoma. Therefore, of the 420 cases, in 250 (59.5 per cent.) there probably was carcinoma present at death. The total group concerning which we have definite information consists of 206 having died of carcinoma and sixty-one (22.8 per cent.) were supposed to have died of other causes, this latter, however, we doubt, as stated above. Thus 206 (77.2 per

TABLE XLIX.—*Duration of Tumor before Operation, with Size of Tumor, 414 Cases (Dead) Carcinoma of Breast*

Size of tumor	Duration of tumor before operation														Per cent.	Total
	3 mos.	6 mos.	9 mos.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs. or more	Unknown		
Very small	1	1	1	1			1								1.2	5
Small	21	13	11	8	18	3	3	3	1	1			3	2	21.0	87
Moderately large	14	13	6	9	13	4	1						4		15.5	64
Large	33	38	31	35	39	16	10	7	2	2	1		9	1	53.9	223
Very large	1	3	5	11	8	1	1								7.2	30
Unknown		2	1	1	1										1.2	5
Totals	70	70	53	65	79	24	17	10	2	3	1		16	4	100.0	414

Six cases were omitted because of bilateral involvement at time of admission.

The classification as to size was made on the basis of the history, physical examination, operative and pathological note. Large size indicated the occupation by the tumor of practically the entire breast. Very large, not only the entire breast but also invasion of the adjoining skin. Six to ten centimeters in diameter was classified as moderately large, and below six centimeters, small; while pea size to three centimeters, and below, very small. There did not seem to be any relation between the size of the tumor and the duration of the disease. It is evident that 33.8 per cent. of the patients came in within six months of discovery of the tumor, 46.6 per cent. within nine months, 62.3 per cent. in a year, and 81.4 per cent. within two years.

TABLE L.—*Classification of the Causes of Death of the 420 Patients Who Had Carcinoma of the Breast*

Carcinoma	Metastases	Local and regionary recurrences *	Causes other than carcinoma	Cause unknown
Opposite breast.... 8	General.... 13	Local and regionary.... 20	Pneumonia.... 10	153
Stomach.... 12	Internal.... 31	R.R.* and internal metastases.... 4	Pulmonary embolus.... 7	
Uterus.... 3	Spine.... 17	R.R. and skin met.... 3	Paralysis.... 5	
Intestines.... 2	Mediastinum.... 7	Breast.... 4	Infection.... 4	
Rectum.... 1	Bones.... 7	Neck.... 2	Other causes.... 3	
Lungs.... 10	Skin.... 1	R.R. and mediastinum.... 2	Senile debility.... 2	
Liver.... 12	Chest wall.... 1	R.R. and glands of neck.... 2	Tuberculosis lungs.... 2	
Œsophagus.... 1	Location unknown.... 4	R. over clavicle.... 2	Bronchopneumonia.... 2	
Location unknown.... 13		Supraclavicular glands.... 1	Shock.... 3	
		R.R. internal met. and opposite breast.... 1	Heart trouble.... 2	
		R. neck and metas. spinal cord.... 1	Gastritis.... 1	
		Mediastinum.... 1	Myoma uterus.... 1	
		Inoperable recurrence.... 1	Diabetes.... 1	
		R.R. and met. central nervous system.... 1	Pneumonia and infection.... 1	
		R.R. and met. lungs.... 1	Myelitis.... 1	
		R.R., whole glandular system.... 1	Hemiplegia.... 1	
		L.R.* and liver and pancreas.... 1	Congestion lungs.... 1	
		R.R. and general met.... 1	Hæmorrhage from recurrence.... 1	
		R.R., pylorus and liver.... 1	Sciatica.... 1	
		R. and pleurisy.... 1	Uræmic coma, multiple neuritis and brain trouble.... 1	
		R. to chest.... 1	General exhaustion.... 1	
		R. neck, axilla and metastases mediastinum.... 1	Cerebral embolus.... 1	
		R. metastases pleura and skeleton.... 1	Tuberculosis, peritonitis.... 1	
		Location unknown.... 9	Apoplexy.... 1	
			Meningitis.... 1	
			Flu.... 1	
			Myocarditis.... 1	
			Osteomyelitis of ribs and sternum.... 1	
			Myocardial failure.... 1	
			Septicæmia, bronchopneumonia.... 1	
			Broken leg.... 1	
Total.... 62	81	63	61	153
14.8%	19.3%			

* R.R.—Regionary Recurrence. L.R.—Local Recurrence. R.—Recurrence.

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TABLE LI.—*The Causes of Death of Patients Having Carcinoma of the Breast, but No Metastases at the Time of Operation*

Carcinoma	Metastases	Local and regionary recurrences	Causes other than carcinoma	Cause unknown
Stomach........ 4	General......... 4	Local and regionary..... 3	Pneumonia.............. 2	14
Opposite breast...... 1	Internal........... 5	Breast.............. 2	Myelitis................ 1	
Uterus........ 1	Bones........... 3	Supraclavicular glands... 1	Hemiplegia............. 1	
Intestines........ 1	Spine........... 3	Whole glandular system.. 1	Diabetes................ 1	
Rectum........ 1			Bronchopneumonia....... 1	
Lungs........ 2	Mediastinum........ 1		Osteomyelitis of rib and sternum. 1	
			Uremic coma, multiple neuritis and brain trouble......... 1	
Total........ 10	16	7	8	14
18.2%	29.1%			

Of the 420 cases of known dead, fifty-five or 13.1 per cent. had no metastases at the time of operation. Of the group of eight cases in which the cause of death was given as other than carcinoma it is probable that in seven of the eight cases the patients had metastases. This information is obtained from the history in which the correspondence from the patient's physician and family were filed.

cent.) of the 267 known group undoubtedly died of or with carcinoma. If this percentage may be applied in a speculative manner to the 153 cases about which no information could be obtained, and it is only reasonable to assume that approximately the same percentage of this group of 153 would be affected as the 206 group, the result shows that 118 would have died of carcinoma and thirty-five from other causes. In other words, of the 420 known dead patients all but ninety-six (22.8 per cent.) died of or with carcinoma. This estimate is very conservative because more patients would be included in the "died of carcinoma" group if of the sixty-one cases supposedly succumbing to other causes there was a reduction from sixty-one cases (14.5 per cent.) to seventeen cases or 4 per cent., as suggested previously. If this reduction

TABLE LII.—*The Causes of Death of Patients Having Carcinoma of the Breast but Who Lived Ten Years or More after Their Operation*

Carcinoma		Metastases		Local and region-ary recurrences	Causes other than carcinoma		Cause unknown
General	1	Mediastinum	1	0	Other causes	1	8
Rectum	1	Internal	1		Senile debility	1	
Lung	1	Pelvic bones	1		Pneumonia	1	
Liver	1				Bronchopneumonia	1	
Stomach	2				Apoplexy	1	
Intestines	1				Heart trouble	1	
Opposite breast	2				Paralysis	1	
Total	9		3	0		7	8

Attention is called to the fact that in this group of twenty-seven patients, or 6.4 per cent. of the 420 known dead, which lived ten years or more after operation, there were no local recurrences. Twelve or 44.4 per cent. of the 27 died of carcinoma. In eight or 29.5 per cent. the cause of death was unknown. Seven or 25.9 per cent. died of causes other than carcinoma. A further study of this group revealed that eighteen cases or 16.7 per cent. of this group of twenty-seven did not have metastases before operation while nine or 33.3 per cent. did have. Fifteen or 55.6 per cent. had the Halsted Thiersch graft operation while twelve or 44.4 per cent. were operated upon by the closed plastic method.

be permitted, then in 93.2 per cent. of the 250 cases the cause of death was probably carcinoma. Providing the unknown group of 153 cases were similarly affected, then 143 patients of this group would have died with carcinoma and only ten without it. Thus of 420 cases all excepting seventy-one patients would have succumbed to or at least with carcinoma present.

As shown in Table LII, in the group of known dead there were twenty-seven patients, or 6.4 per cent., that lived ten years or more. Of this group twelve (44.4 per cent.) died of carcinoma. Seven or 25.9 per cent. succumbed to other causes, while in eight or 29.5 per cent. there were insufficient data. In all probability in some individuals in these two latter groups carcinoma was present at the time of death. It is to be recalled that in one of Doctor Halsted's cases there was at the time of death a carcinoma of the liver thirty-two

Bar Diagram U

The Percent of Local Recurrences After Operations for Carcinoma of the Breast by Eminent Surgeons in Various Countries from 1867-1931

OPERATOR	TIME	NO. OF CASES	LOCAL RECURRENCES
BERGMANN	1882-87	114	51-60 PERCENT
BILLROTH	1867-76	170	82 PERCENT
CZERNY	1877-86	102	62 PERCENT
FISCHER	1871-78	147	75 PERCENT
GUSSENBAUER	1878-86	151	64 PERCENT
KONIG	1875-88	152	58-62 PERCENT
KUSTER	1871-85	228	59.6 PERCENT
LUCKE	1881-90	110	66 PERCENT
VOLKMANN	1874-78	131	60 PERCENT
HALSTED	1869-98	133	27.1 PERCENT
HALSTED	1869-94	50	6 PERCENT
HALSTED	1889-94	50	31.9 PERCENT
HOPKINS HOSPITAL	1889-1931	447	32.2 PERCENT
HOPKINS HOSPITAL	1889-1931	541	26.6 PERCENT
HOPKINS HOSPITAL	1889-1931	950	15.2 PERCENT

(PERCENT axis: 0 10 20 30 40 50 60 70 80)

The percentage of local recurrence reported by Halsted by 1898 was as shown, 27.1 percent. Of these original 50 cases in which were reported 6 percent local recurrences in 1894 have now been found in 1931 to be really 31.9 percent. The percentage of local recurrence at present in the Johns Hopkins Hospital is dependent on the way in which they are calculated. If the entire series of 950 cases is taken into consideration, which includes those cases lost track of, then the percentage of local recurrence is 15.2 percent. If, on the other hand, the known dead group of 419 cases, eliminating one case in which there was insufficient data, is taken into consideration with 28 additional cases in which there was known to be a local recurrence, making a total of 447 cases, of which there were 144 local recurrences, then the percentage of local recurrence comes to 32.2 percent. On the other hand, when one considers the group of 419 known dead plus 28 in which there was a known local recurrence, in addition to 94 patients living and well, the total number comes to 541, of which 144 had a local recurrence, making a percentage of 26.6 percent for the local recurrence in which all the patients of the Johns Hopkins Hospital that were operated upon are included excepting 209 cases of those which have been lost track of. This it seems to us is a more true representation of the incidence of local recurrence.

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years after operation, during which time the patient had enjoyed good health.

The conclusion that the large majority of patients affected with carcinoma of the breast will succumb to this disease is therefore unquestionably warranted. We also feel that this study establishes the fact that a large number of patients are free from *clinical cancer* for a varying number of years following operation, but whether or not a patient is ever completely cured (*in the pathologic sense*) of carcinoma is open to question. Undoubtedly, if operated upon properly the condition may be cured locally, and that is the only point for which the surgeon must hold himself responsible.

It is, of course, always possible that the disease may still remain a localized process which has not spread beyond the limits of operability, and especially is this so in the very early cases that come under observation today. In view, therefore, of our inability to foretell the exact limits to which the disease has spread, a thoroughly radical removal should be done in all cases whether early or late. It is a well-known and proved fact that patients from whom the primary growth has been removed and who have lived without symptoms of *clinical* cancer for many years afterward, finally succumbing to some other malady, were found to have regional metastases in which microscopical carcinoma could readily be demonstrated. (Peugniez' case*.) It would also seem that carcinoma may vary not only in its rate of growth but as well in its damaging clinical effects when the cells are removed from their primary site to a different type of tissue, such as a lymph-gland or another organ. This idea receives additional support from the observation that the post-operative longevity of patients without local recurrence is greater than of those with a reappearance of the growth in the operative field. This is true despite the fact that in both there may be remote metastases.

Hence it follows that, *regardless of the extensiveness of the disease, so long as it remains confined within possible operative limits, it is incumbent on the surgeon to perform the most radical and meticulous operative procedure, including a far wider exsection of skin than has been customary, in even the Halsted Thiersch graft procedure as performed in the majority of instances in the past, for it is only by this method that the proper amount of skin and subcutaneous tissue will be sacrificed. There alone exists the possibility of reducing local recurrence to a minimum.*

Peugniez, in 1899, operated upon a patient, removing practically all of the stomach, thus performing a very radical subtotal gastrectomy. The patient died in 1925 of lobar pneumonia at the age of seventy-seven. The post-operative life was thus a period of twenty-five years. Examination of the stomach which was removed at the time of operation proved the condition to be carcinoma and autopsy twenty-five years later revealed the retro-peritoneal lymph-glands and the liver both involved in carcinoma whereas the remaining portion of stomach was normal. This patient, however, was cured of clinical cancer, although still infected with microscopical cancer.

* Peugniez, P.: Une gastrectomie pour cancer remontant a vingtequatre ans. Bull. Acad. de Méd., vol. xcii, p. 831, Paris, 1924.

CANCER OF THE BREAST*

THIRTY-TWO YEARS' EXPERIENCE

By Edward J. Ill, M.D.

of Newark, N. J.

THE importance of the subject to be considered is shown by the fact that 39.3 per cent. of the total mortality from cancer in the female is due to cancer of the breast. This mortality is taken from an analysis of thirty-one thousand deaths.

In 1924, I was discussing the end-results of cancer of the breast with a very good surgeon. He remarked sarcastically that he had had eighty-eight cases and eighty-eight deaths in less than the five-year period. This study was prompted by the query, Have you ever seen cases remain well after the operation? Since this date (1924) I have been constantly looking out for the end-result, as old patients presented themselves or as correspondence gave some information. At that time I have been told that reliable statistics of the operation in regard to the ultimate operation outcome of cancer of the breast are rare. I noticed that some one said, "All die in the 5-year period." It seems to me that the outlook should be getting better in the hands of the conscientious surgeon. Thanks to the efforts of the American Society for the Control of Cancer, cases are coming earlier to us. I can now present the study of thirty-three years of surgery for cancer of the breast. It has taken me seven years to compile these records and thus to be in a presentable condition for study and report.

When Halsted reported his first operation for cancer of the breast in the ANNALS OF SURGERY in 1898 I was much impressed with his work.

An immediate study of the anatomy of the breast in its relation to the pectoral muscles, the subclavian vessels, the lymphatics and nerves and axillary tissue, was made. It all looked so scientifically correct as dissection after dissection on the cadaver was made. All the cases operated on and reported in this paper followed exactly the description given by Doctor Halsted, except in two where Jackson's incision was made, hoping to leave a less tender scar. In this I failed and promptly returned to the original operation of Halsted. I have never changed from this operation. I have not made my patients experimental guinea-pigs, for I well knew that years must elapse before one can come to a decided conclusion.

The operation of starting the dissection in the axilla never appealed to me for reasons that would take too long to discuss. There are some fundamental principles involved in the operation, as I look at it now after many years of study and observation. They seem to me of the utmost importance:

Fixed involvement of the axillary glands, and, when it can be made out,

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* Read before the Practitioners' Club of Newark, November 2, 1931.

of the subclavicular glands, are no longer cases for operation with the view of cure. I have had many cases, however, go on over the five-year period with movable glands.

Dr. James Ewing agrees with this view and once said: "Surgeons will have to change their indication on these cases or they will dishonor their calling." His prognosis was a shortened life and in this Doctor Ewing is surely correct. I had long ago come to the same conclusion.

We may be called upon to operate as a palliative measure but the result will surely shorten the patient's life. Supraclavicular involvements are an absolute contra-indication for any operation because secondary involvements may with confidence be looked for. X-rays of the chest and the bones of the arms will usually satisfy our curiosity and prevent a useless and harmful

CANCER MORTALITY BY ORGANS AND PARTS FOR MALES AND FEMALES
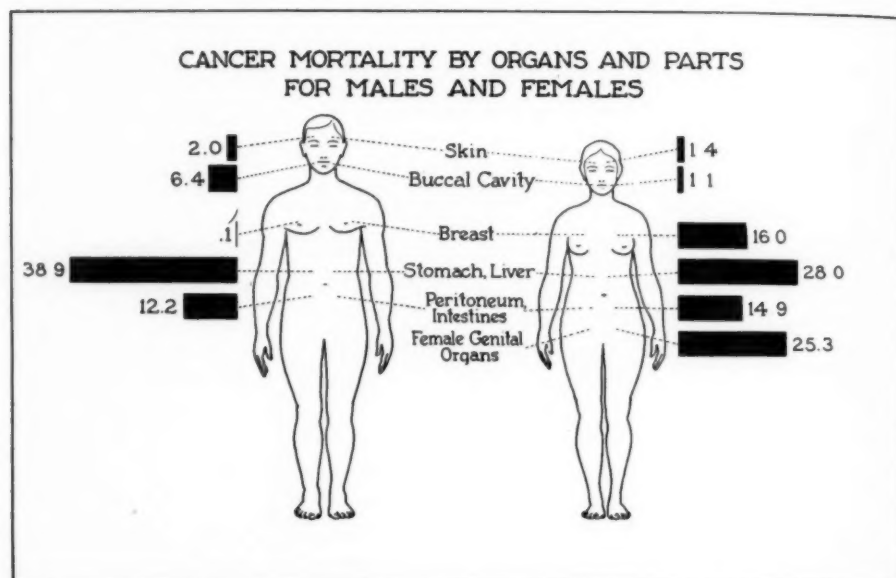
FIG. 1.

operation. In the pre-Halsted days I often resected parts of the clavicle, which was invariably followed by an early local and general recurrence.

Œdema of the skin ,if it is not due to an abscess, shows an extensive involvement beyond the local area and seems to me to be a contra-indication for any operation. Fischer calls this subepidermoidal carcinoma.

The incision should be wide from the tumor area, giving a large space to work in and at the same time keeping wide away from the tumor. It should begin at the bicipital ridge of the humerus. Early in my work I did much transplantation of skin but of late hardly any, and then only in very thin women. It is rather important to make an incision through the skin and fat from the insertion of the scalenus muscle into the clavicle, to the upper part of the circular incision around the breast. This allows a very great abundance of working space under the clavicle. The skin

incision far from the cancerous nodule probably accounts for the very few lical recurrences noticed in this study.

The skin should be dissected from its underlying tissue away from the tumor far in every direction, leaving a good portion of fat with the skin; otherwise, sloughing will result. The incision should be carried down to the chest wall and pectoralis major muscle everywhere, except in the axillary and lateral chest wall, where the dissection is made from within out, severing the whole mass after all the subclavian and axillary glands, still attached to the breast, are removed, and *removed in one piece.*

It is of the utmost importance that we now cut the pectoralis major from the bicipital ridge and carry the dissection to the chest wall. The muscle is cut away from the chest wall and thus is exposed the pectoralis minor muscle. Any areolar or fascial tissue on the minor muscle is dissected upward and the muscle is then cut across. All the subpectoral vessels are ligated and we now have the whole subclavicular and axillary space before us. It is also important that any fat or glands should not be separated from the vessels except as part of the original tumor. A gland left in and dug out separately spells early death to the patient, always provided that such a gland is cancerous. I shall come to this again later on.

Ligation of all the vessels should be made with very fine catgut—No. oo— at the end of every step, excepting the large subpectoral vessels. Double ligation of all the veins and arteries coming from the subclavian and axillary vessels should be made, severing them between the two. This is strongly urged because any bloody infiltration of subclavicular and axillary cellular tissue makes a fine dissection impossible.

The dissections in the axilla should be carried on backwards and outwards until the teres major, the subscapularis, and the edge of the latissimus dorsi are in sight. The external thoracic nerve need not be sacrificed. I notice that the axillary fascia is often lost sight of. If we remember that it begins at the outer edge of the pectoralis major and corococlavicular fascia in front and extends to the lower border of the latissimus dorsi behind, we shall not go wrong. Both structures must be cut and *removed in one piece with the original mass.* The loose areolar tissue makes blunt dissection easy, always pushing the vessels from the surrounding tissue, and not the reverse. The serratus magnus is always plainly in sight at this time. The thorocoacronial artery and the lateral thoracic artery and veins should be ligated doubly so as to stop any return flow of blood. Often enough the subscapular artery and vein arise high up on the axilla and need a double ligature.

After removal of the tumor mass, careful treatment of even the smallest bleeding point is indicated. Closure of the wound with interrupted or continuous suture of No. 1 catgut is made. Where there is any tension a figure-of-eight suture of silkworm is done. If it is found that these sutures are inefficient, bone plates or metal plates can be used. Stab-wound drainage has been my choice. If radium is to be applied large tubes of rubber are advisable, all to be removed in twenty-four or thirty-six hours.

It is most important to remove all the lymphatic and areolar tissue in the subscapular subclavicular and axillary space in one piece connected with the original tumor. Any incision between cancerous glands and original tumor makes for a gloomy prognosis and death at an early date. It is remarkable, however, how often one finds glands that are not malignant.

I am under the impression that post-operative radiation of X-ray and radium, when cancer glands were found and not expected, has given the patient longer life. I have in mind a lady operated on ten years ago with a large bunch of subclavicular infiltration, who is today entirely well, and another who with supraclavicular recurrence is well now after four years. This subject, however, will have to be the object for further studies.

Doctor Pfaler says that "radium is a most useful agent in the treatment of palpable recurrent or metastatic nodules from carcinoma of the breast." It will be right to talk of biopsies here. I am often glad to have the opinion of the pathologist at this time, well recognizing the fact that in the hurry with which a frozen section is made serious errors are likely, and do occur. If the error occurs, and it is often unavoidable, an early death is likely. I have in mind the case of a woman, who died in eight months, when the report came ten days later that she had a cancer. On the other hand, I have removed a carcinoma under misapprehensions, followed the primary operation in ten days by a radical one and the patient is living, fifteen years later, and still well.

When a biopsy shows a cancer, the wound should be swabbed with pure carbolic acid and tincture of iodine, equal parts, and sewed up—*absolutely tight*. The area of operation should then again be disinfected, all instruments, towels, gloves and gowns changed, and the radical operation proceeded with.

The cause of cancer of the breast has been the study of many. A blow is usually given as an inciting cause and I think it may be so, as my histories often enough say. On the other hand, the breasts are prominent organs and subject to external insult. For years I have been questioning my patients on the subject of chronic mastitis preceeding cancer, and have thus far seen but one definite case. Chronic mastitis is exceedingly common. Papillary duct cyst adenoma shows to be cancerous in about one out of fourteen or fifteen cases in my experience, and this should be borne in mind.

Cancer of the puerperal breast is rapidly fatal and has been so in my hands.

Those who have made a study of records extending over many years know of the very great difficulty encountered. It is now seven years since a follow-up system has been pursued. It surely was exceedingly difficult. Facts had to take the place of impressions. Many a surgeon operates when in his heart he does not know if he is doing harm or good. Some of my cases had poor addresses or had moved away, many letters being returned unopened. Some have come at my invitation, as many as twenty in one morning. Many have answered letters. In some cases I learned through

relatives of deaths and this was corroborated by a study of the records of Vital Statistics in Trenton. Some have turned up for other troubles and being well did not understand why they should answer my letter. I have searched the statistics of the Vital Department at Trenton for those whom I could not trace otherwise. This gave me some interesting and surprising information. Of this, more later. In this report I find that I did the Halsted operation 266 times in thirty-two years, *i.e.*, up to January 1, 1930. Those operated on since were too recent to draw any deduction from, there being seven such cases, all well at present.

Among these, 175 were married, 48 single, and the rest were not noted, This means that the records show 3.6 as many married women have cancer of the breast as single ones. It looks like a preponderance of the disease in the married. When we remember, however, that 20 per cent. of all women after thirty-five years are single it immediately becomes apparent that cancer of the breast is more frequent in the unmarried woman.

Doctor Summers, of Omaha, says that the relative proportion in the death rate is 44 per 100,000 population for the married as compared to 109 per 100,000 in the single. (In the October, 1931 number of Surgery, Gynecology and Obstetrics.)

There were twenty-three cases where the address was so bad that no search was made. 135 letters were returned and the cases could not be traced. Often enough the attending physician would not remember the case. Forty-seven cases lived over five years. Among these there were: Five who lived six years, two who lived seven years, three who lived eight years, two who lived eleven years, one case each who lived twelve, twenty-one and twenty-four years respectively, and, seven who died from causes in no way of a cancerous nature in from three to sixteen years.

This makes altogether fifty-four cases that had no recurrence or about 20 per cent. of what I call five-year cures.

If I add to the above forty-four cases recorded in the Department of Vital Statistics at Trenton as living and seven as having died from other causes I find that the ultimate recoveries are over 30 per cent.

Among my personally kept records there were five cases well at the end of four years and three years respectively and two were well at the end of two years. Forty-four cases died of cancer in less than two years. I have had a recurrence in the scar five times.

Because of the large number whom I could not trace I searched the records of the Vital Statistics in Trenton with the following interesting result. I searched for the names of 102 patients. Of these there was no record of death in forty-four cases. Now they either left the state or else are living and well at the present time. The search extended from 1899 to 1929, inclusive. I find that twenty-six are reported as having died from cancer of the breast in anywhere from four months to nine years after the operation. Many (11) died in the first year.

I found three as having died from tumor of the brain, likely cancerous in seven, one and two years from the time of operation.

Cancer of the lung is reported in six cases, four in one year and one in five and two years respectively. Two cases died of cancer of the liver within one year. One case died of cancer of the uterus in three years. One is said to have died of cancer of the sacrum in two years and one each of cancer of the pancreas and stomach.

The foregoing forty-one cases, or 40 per cent., surely died from cancer in one form or another. There were some doubtful reports, thus: One is said to have died of anæmia in one year, which was likely cancer. One died of myelitis in four years, which was surely cancer of the spine. Acute bronchitis in a woman of forty-six years, two years after the operation, is doubtful, as is also a tuberculosis of the lung in the same length of time. There was one death from cardiac disease in five years, three due to chronic Bright's in six, five, one and three years respectively. One each died from lobar pneumonia and suicide in six years. One had apoplexy in four years at the age of seventy-seven years, and another in five years. There was also one reported as having died from senility at seventy-seven years, thirteen years after operation.

To sum up, I find that forty-one had cancer, four were doubtful but likely cancer, and eleven that could not be called cancer by any stretch of the imagination. Forty-six cases, then, lived without a recurrence of cancer.

It is right that I should say that three cases were done which showed no cancer. I am, however, not discussing the diagnosis of cancer of the breast except to say that the best of us have gone astray. Our diagnostic shortcomings must, however, not make us sacrifice a whole breast for an innocent tumor. I also wish to say that secondary operations are worse than useless.

A few cases of excision of the subclavian or axillary veins were done. All patients died within the year. Wound of the subclavian has occurred once and was relieved by fine silk sutures.

Two patients died, one from hæmorrhage into the cellular tissue and the other one from acute dilatation of the stomach, making 0.8 of 1 per cent.

I have been struck during my searches of the many cases where other cancers have occurred in the same family—once four cases in the same house and family within twenty years.

A removal of the second breast occurred in five cases, after an interval of six, one, one, one and three years, respectively. We note recurrences in the lung fifteen times, extending from one to twenty-one years, in one case after six years, there having been an axillary infection.

We had cancer of the spine in four cases and of other bones three times. One case of cancer of the spine who was bedridden is again up and about after six months' treatment with selenium. She is among the above four cases and the original operation was fourteen years ago. There was cancer of the long bones and of the lung twice. We record cancer *en cuirrasse* but once. Three times we heard of spontaneous fracture of the long bones and once fracture

of both radii and femur after three years. We saw a carcinoma of the vagina after eight years. We judge that this was a new infection since this was of the squamous variety. Once I attempted to remove the glands of the supra-clavicular space with the result of a wound of the thoracic duct, which, how-ever, closed up in a few days. She died shortly of the disease. In one case we got a severe infection but the patient got well and remained so for over eight years, and is still well. · In one case we had a recurrence in the axilla in fifteen years. We note five cases where glands were infected and life was prolonged for twelve, eight, three, eight and seven years respectively and all are still living.

I did extensive skin grafts three times in my early work. I have learned to avoid this.

Hopeless cases to start out with I have not operated on, except in rare instances, where ulcerations produced great pain or foul discharge and then it was a simple amputation.

In all, I noted sixty-one recurrences in from eight months to twenty-one years, in my personal experience, there being: two in eight months, one in nine months, eighteen in one year, fifteen in two years, six in three years, two in four years, three in five years, four in six years, and one each in eight, nine, ten, eleven, twelve, thirteen, fifteen, nineteen and twenty-one years.

In ages they range from twenty-seven to seventy-seven years. I have seen many cases of atrophic cancer in women older than eighty but thought they would live longer if let alone. In this opinion I was borne out by a few cases and an early bad recurrence when operated on by others.

As to their ages, there were three in the twenties, twenty-three in the thirties, ninety-four in the forties, seventy-seven in the fifties, forty-nine in the sixties, and twelve in the seventies, making a total of 256.

In three cases no age was given and seven occurred since January 1, 1930. I was wondering if the forties showed an increase of cancer over the fifties, and looking up the statistics of the census bureau of 1920 of the United States Government, I find that the number of women in the forties is 6,403,093 and in the fifties is 4,413,610. In other words, there are 2,000,000 more women living in the forties than in the fifties, which would indicate that there are relatively 33 per cent. more cases of cancer of the breast in the fifties than in the forties. This is borne out by the number of deaths from cancer of the breast in the registration area of this country for 1928. Percy, in a report of 203 cases, reports the average age to be fifty-three years in the registration area. There are 1,770 deaths in the forties as compared to 2,603 in the fifties —again practically 30 per cent. more.

Now that we are having so large a colored population in the North it is of interest to know how many colored women die of cancer. Again the census of 1928 speaks of 9,208 white women dying of cancer of the breast, but only 624 colored. In my own experience I have not operated on a colored woman, but I have seen one in the practice of a colleague. It is to be remem-bered that about only 10 per cent. of our population is colored. In other

words, there are two-thirds as many colored who have cancer of the breast as white, considering the relative number of both. In a paper written by Doctor Matas in 1896, he definitely says that 'the Negro does not enjoy the immunity to malignant disease which has been heretofore supposed." Doctor Hoffman, in his book on "Mortality of Cancer Throughout the World," speaks in a like strain. That there is less among the Negro we all agree upon. In the male Negro, however, cancer of the breast is twice as frequent as in the male white.

Through Doctor Hoffman's reports valuable statistics are available in regard to the increase of cancer during the past few decades among various peoples and races.
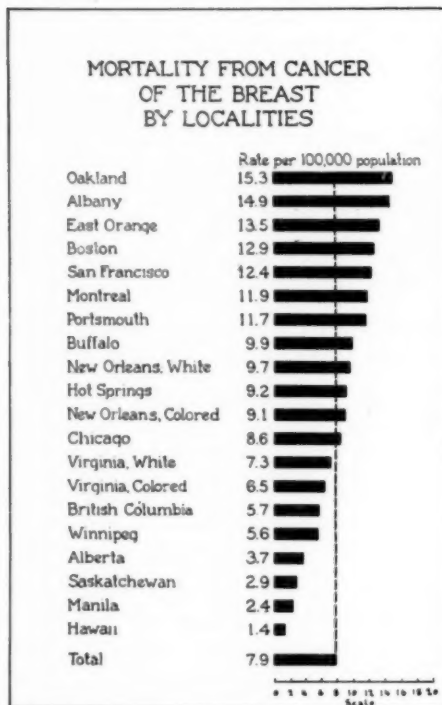
FIG. 2.
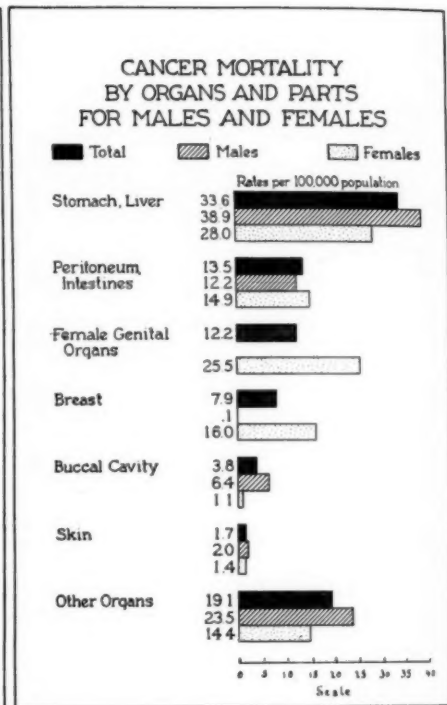
FIG. 3.

The mortality of cancer of the breast in the registration area of the United States in 1927 was 9,580 and in 1928 was 10,056, or an increase of 470. It is of interest to know that the "proportion of deaths from cancer of the breast in the mortality from cancer in all forms has changed only from 9.1 per cent. in 1920 to 9.2 per cent. in 1928. It has remained practically the same. We also learn that the death rate per 1,000,000 population in England was 158.4 in 1901 as compared to 1,957 in 1929. There is a very considerable increase in Australia. It has increased by 211 in ten years per 1,000,000, but then the female population has increased in that time by 600,000. There has also been a marked increase in San Francisco of twenty-two cases.

Patients with cancer of the breast live longer, being an average of thirty

months as compared with all other forms where it was only twenty months. This fact must be considered in our aspect as to whether we really prolong the average life by operation. It is interesting to know that cancer of the breast is 8.8 per 100,000 for the country at large while for the state of Maine it is 12.8. No explanation is forthcoming for this remarkable discrepancy. Of course, some single sections have a less mortality, like Florida, where it is only 3.8 per 100,000. Statistics also show that cancer of the breast in the male is less than 1 per cent. of that in the female and that the average age of the male is twenty years more than the female. The exact figure is seventy-five years in the male to 55.8 in the female. These figures repeat themselves again and again. Even in such widely separate locations as San Francisco and New Orleans, where the population is so different, do we find this dissimilarity. The only exception I find was in Chicago, where the average age was fifty-nine years. I know of only one male, a physician, who had cancer of the breast at seventy-five years.

It is well known that certain less civilized people are less subject to cancer than those of a higher type. There is comparatively little cancer of the breast in the Japanese, the Hawaiian Islanders and the American Indians. Doctor Hoffman has never been able to trace a case of cancer of the breast in an American Indian, though they do die from cancer of other organs. What the explanation may be I am unable to say. The increase in cancer of the breast has been remarkable in Canada, being 4.5 per 100,000 in 1914 to 9.2 in 1923, an increase of nearly 5 per 100,000 in nine years. There can be no question about the increase of cancer of the breast at least. In Hamburg, Russia, and Sweden it rose from 39 in 1917 to 53 in 1921 per 100,000. In Holland it rose from 30 cases per 100,000 in 1905 to 40 in 1920. Why Hawaii should have so low a rate of cancer of the breast as 3.3 per 100,000 is a question of great interest.

In closing I want to say that there is a great move to give up the surgical removal of the diseased breast for the treatment with radium or X-ray. While I have seen some good results I have not yet been able to assure myself that I want to give up the early cases for the newer method of treatment. It has taken three decades of surgical experience in my hands to come to some conclusion. The advocates of the newer treatment will have to show many years of experience before definite conclusions can be reached.

THE RESULTS OF TREATMENT OF MAMMARY CARCINOMA

By Surgical and Irradiation Methods at the Memorial Hospital, New York City, During the Decade 1916 to 1926*

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of New York, N. Y.

ATTENDING SURGEON TO THE MEMORIAL HOSPITAL

THE medical profession has been and still is attempting to evaluate irradiation therapy in cases of mammary carcinoma. Surgeons in particular have urgently asked for an answer to the query, "To what extent may irradiation be relied on, in the cure of mammary cancer?" The study herein reported is made in an attempt to answer this question. Many inquirers have become discouraged waiting for the satisfactory answer to arrive. However, it will eventually come. The dissatisfaction is due to the following reasons:

First, the over-enthusiastic reports of certain observers have definitely closed the mind of some to a belief in ANY report on the value of irradiation, no matter from what source.

Second, the constantly changing irradiation technic, with its resultant changes in statistical results, has led to great confusion as to what are the exact end-results.

Irradiation is the youngest of the medical sciences. It must therefore follow that there will be innumerable and constant changes taking place until it is finally decided which of the many technics, methods of applications, types of filters, voltage, *etc.*, are best suited for a particular case. This takes *experiment, experience* and *years* to work out. The information seems long in coming—AND CORRECTLY SO; but it is impossible to incubate facts and bring out correct conclusions. Irradiation methods have changed so rapidly during the short career of this science that by the time one method has been thoroughly tested over a period sufficiently long to report five-year results, a new technic has been developed which completely replaces the former. This is obviously highly unsatisfactory to the physician who seeks exact information on the reliability of irradiation treatment, but also equally unsatisfactory to the physician who is working in the field where irradiation is employed either as a complete method of therapy or as an adjunct to surgery. Moreover, the shifting status of end-results of the irradiated cases unfortunately opens wide the door for over-statement by the unscientific or the unscrupulous enthusiast. The final word on irradiation results cannot be voiced today. There is every probability that years will pass before the ideal technic and the ultimate method shall have been settled. As a corollary, many of the methods of treatment herein employed will be subject to change with the passage of time.

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* Read before the New York Surgical Society, March 25, 1931.

In the meantime, the fact is being commonly accepted and rather widely adopted that irradiation has an important position in the armamentarium of attack against mammary carcinoma.

It should be stated in the beginning, however, that as a general rule mammary cancer is not so radiosensitive[1] nor so efficiently treated by any of the irradiation methods as cancer in certain OTHER organs such as carcinoma of the cervix, basal-cell epithelioma of the skin, transitional epidermoid carcinoma of the nasopharynx, *etc.* There are exceptions, however, to this general rule, as evidenced in the occasional case of mammary cancer, which, under a few treatments by irradiation, *completely disappears.*

To cure mammary cancer as a rule it becomes necessary to employ interstitial doses of radium as well as external irradiation by the radium packs, or the high-voltage X-rays. In general, we have given up our attempts to treat this disease by external irradiation alone; we usually fail with this, although there is an occasional exception (see Fig. 2 and Case III, following). It requires heavy and prolonged irradiation by both interstitial and external methods to hold mammary cancer in abeyance to the point of "five-year cures."

The Surgical Treatment.—The end-results of surgical treatment have been especially studied during the past forty years since the introduction of the radical amputation by the methods of Halsted and Willy Meyer in 1894. This new procedure increased the "five-year cures" far above the older and commonly used method of the simple mastectomy. The "five-year cures" by the radical mastectomy of *operable* mammary cancer in the well-known clinics of the world are familiar to all. In general, they vary between 32 per cent. and 39 per cent. My belief is that those reports giving much higher cure percentages are to be looked on with suspicion. The following table is sufficient to show a few of the five-year results in some of the American clinics.

TABLE I

	Per cent.
Greenough and Simmons (Huntington Hospital)	32
Moschcowitz (Mt. Sinai Hospital)	34
White (Roosevelt Hospital)	36
Sistrunk and McCarty (Mayo Clinic)	36
Lee (including pre-operative and post-operative irradiation) (Memorial Hospital)	39

It is our impression that there has been but little actual improvement during the past forty years in the surgical technic of the radical amputation. No important procedure has been developed or added, since the fundamental principles were originally laid down by Halsted and Willy Meyer; and no better radical amputation is performed today than that careful and exact operation done by these men years ago. We can, therefore, today take the results of radical mastectomy done by good surgeons as largely a settled surgical problem. Thirty-five per cent., however, as average "five-year cures," is FAR from satisfactory. It seems that out of every three radical

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amputations performed on the *operable* cases but one patient survives the five-year period, while two patients do not. It is this cruel fact which impels the surgeon to hunt *elsewhere* than surgery for assistance. The radical amputation is developed up to the point where no further step can be taken in the way of a MORE radical amputation unless the interscapulo-thoracic amputation is performed, sweeping off all the axillary, supraclavicular and post-clavicular tissues with the arm, scapula and clavicle. I am convinced that this procedure would further improve our operative cures; but it is mutilating and would add greatly to the operative mortality. Is this a justifiable operation? At present our operative mortality from the radical mastectomy is practically nil.

The results of surgical treatment are a matter dependent upon dissemination and metastasis. In an analysis made by White[2] in 195 operable cases, he found seventy-seven cases (38 per cent.) had clinical axillary disease present, but when a careful microscopical examination was made of the axillary contents, 109 cases (51 per cent.) proved to have axillary metastasis. As long as the disease is confined to the breast I think there is at present no more effective method of cure than that of the radical mastectomy, which yields approximately 70 to 80 per cent. But when the disease has left the breast and gone into the axillary nodes or into the loose areolar tissues of the axilla, then the percentage of cures is strikingly reduced, and varies between 15 and 25 per cent. This depends on whether the axillary nodes involved lie in the outer and lower portion of the axilla or at the axillary apex. These figures represent a great failure on the part of surgery to cope with the cancer problem after the disease is present in the axilla. As the disease is present in the axilla in slightly over half of the cases (51 per cent.) we must seek for some method which will compensate for the fiasco of our surgical results in cases where the axilla is involved. The only agent on the horizon that seems to offer encouragement is irradiation.

Criteria of Operability.—It is necessary in order to understand statistical studies to know the exact factors that the author applies to the cases. The definition of operability varies with the individual surgeon. If the patient has an *operable* mammary carcinoma we mean that clinical cancer is limited to the breast; or the breast and the axilla. Any extension of disease beyond the axilla into the supraclavicular fossa or into the liver or chest or to distant parts is considered to be *inoperable*. An X-ray plate of the chest is taken in every instance and evidence of extension into the hylum lymph-nodes or along the bronchi will immediately classify it as an inoperable case. The liver is carefully examined routinely and if there is enlargement, nodulation, or jaundice, the case is likewise considered inoperable. The patient is always asked if any pains in distant portions of the body are present. If the patient complains of pain in one or both knees, down one or both thighs, or in the back, films of the pelvis and spine are taken for evidence of bone metastasis. Examination is made for nodules which may be scattered in the skin about the affected breast. The opposite breast, axilla and supraclavicular region

are examined. If the diseased breast is red, having an elevated temperature with a sharp line of demarcation rather suggesting erysipelas, careful consideration of "inflammatory carcinoma" is made. This clinical type of carcinoma was described by Lee and Tannenbaum.[3] "Inflammatory carcinoma" is a totally inoperable type because the dermal lymphatic spaces are plugged with clumps of rapidly growing cancer cells and it is practically impossible to circumvent the disease by operation.

If the axillary mass be very bulky or fixed, the case is considered inoperable even though no supraclavicular nodes are yet palpable. Even in the absence of supraclavicular disease, if the patient complains of pain radiating down the arm of the involved side the probability is in favor of a beginning carcinomatous invasion of one of the chords of the brachial plexus and the case should be classified as inoperable.

Carcinomatous skin nodules surrounding the breast and extending to the sternum make it improbable that there will be a reasonable likelihood of operative cure. In such a case the skin is so widely invaded that the intercostal lymphatics have usually carried the disease through the pleura into the mediastinum and chest even though the X-ray may fail to demonstrate it. *Fixity* of the tumor to the chest wall as a rule signifies inoperability, but not always; much depends on the *degree* of fixity.

It appears almost superfluous to state the criteria of operability. One, however, is not infrequently shocked to see a patient who has a recent operative scar present supraclavicular disease; or complain of pains in the spine or pelvis; or whose X-ray of the chest reveals a definite evidence of intrapulmonary disease. Any one of these conditions demonstrates that a judicious pre-operative estimate of the operability of the case was not made.

It often happens that an operable mammary cancer is present in a patient who has a co-existing disease of such significance or severity that an operation is definitely contraindicated. Some such conditions are diabetes, nephritis with high blood-pressure, tuberculosis, cardiac diseases, old age, *etc*. In the management of such cases it is imperative that we have exact information on the degree of reliance to be placed on methods of therapy *other* than surgical.

Like other hospitals possessing large equipment of radium and X-rays, Memorial Hospital has been making a sincere attempt to evaluate irradiation therapy. The hospital staff is in a position to observe great numbers of cancer patients. In recent years there are annually admitted to the Breast Clinic about 550 cases. This affords opportunity of treating breast cancer by irradiation, by surgery and by the combination of surgery with irradiation.

Surgical Methods Versus *Irradiation Methods.*—If one is to completely comprehend the problem, one must keep in mind that although the *end-results* to be accomplished by surgery and irradiation are identical, namely, to *cure* the patient of a cancerous disease, still, *the methods of accomplishment have not one thing in common.*

The *surgical* method of treating mammary cancer aims at the absolute eradication of the entire disease process by a wide, careful, radical extirpa-

tion of the breast, its contiguous tissues and its drainage basins. As a rule, the surgeon has but one opportunity to ever cure the patient. If recurrence follows the operation, which it does in approximately 65 per cent. of the operable cases, surgery is relegated to the realm of an improbable cure.

The *irradiation* method aims at (*a*) devitalizing the cancer tissue and (*b*) at the same time changing the character of the surrounding tissues or the "cancer bed" into a firm, fibrotic and occasionally even a calcific mass, thereby gradually strangling, starving and rendering the cancer cells impotent of cell division and metastasis. In a general way this process is comparable to the ideal result of a properly treated tubercular lesion. In tuberculosis, the bacilli are enmeshed within the tubercle, and surrounded by dense, fibrous and at times calcified tissue. The tubercle bacilli are locked up within a fibrotic and stony prison. The *aim* in irradiation is really identical—to lock up the disease. It takes patience and time to achieve this aim as it likewise does in tuberculosis. Certain cell changes take place in the cancer tissue, such as hydropic degeneration,[4] nuclear fragmentation, cellular disintegration, *etc*. Simultaneously, the "cancer bed," or normal surrounding tissue, under the influence of irradiation, is going through the slow changes of hyalinization, obliterative endarteritis, fibrosis, mononuclear infiltration, calcification, *etc*. The result is a direct killing effect on a proportion of the cancer cells, and a locking-up of the cancer in a fibrotic mass. Some of the disease is virtually still present for years, and, under proper circumstances, can be relighted, just as is true of healed tuberculosis. To accomplish this ideal of permanent cure in the treatment of cancer by irradiation, an *exact* technic must be worked out. This can be attained only by allowing a generous period of time for the mutation of tissues. Great patience is required of the therapist. It is a virtual race between the growth processes of the cancer, and the locking-up processes of the cancer bed. If the rapidity of cancer growth occurs at a faster rate than the building of the prison by the elements of the cancer bed, the patient will succumb of his disease. On the other hand, if the cancer bed strangles the cancer by an excess production of fibrous tissue, and the cancer cells are starved by endarteritis and a diminished food and blood supply, then it follows that the disease must remain a local process. We have many cases with the complete scientific data to prove this point; cases that have remained "cured" or locally inert for many years.

The following three cases illustrate patients in whom the mammary cancer has been inactivated by proper irradiation therapy. Each one of these three cases has cancer cells present in the fibrotic mass. They have been present since commencing the original radiation therapy: six years, six months; six years, six months; six years, four months ago. Experiences with such cases will eventually point the way to the ideal to be striven for in the irradiation therapy factors. One must not be discouraged by the fact that the microscopical studies reveal the presence of cancer cells, even though they be viable cells. Some observers have condemned the use of interstitial and external irradiation in the treatment of mammary carcinoma, because

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their microscopical studies show these cancer cells present; but this view-point is unjustified by the subsequent clinical course of these same patients, as the following cases illustrate:

CASE I.—R. S., married female, of sixty-five years came to the Memorial Hospital December 18, 1924. (See Fig. 1.) The patient had noted this lump in the right breast for a period of a year. It measured 3 by 3 by 2 centimetres. No definite nodes palpable. Chest plate negative for metastasis. In brief, this breast received: 900 millicurie hours by insertion of platinum radon needles into the breast tumor. 3,000 millicurie hours by radium tray over the lesion. Thirteen low-voltage X-ray treatments. Eight high-voltage X-ray treatments.

These treatments covered a period of three and one-half years. No biopsy was ever made until March 20, 1931, when a Hoffman punch biopsy was taken. The report of the pathologist was "carcinoma on the smear. Confirmed on section. Cells small, hyper-
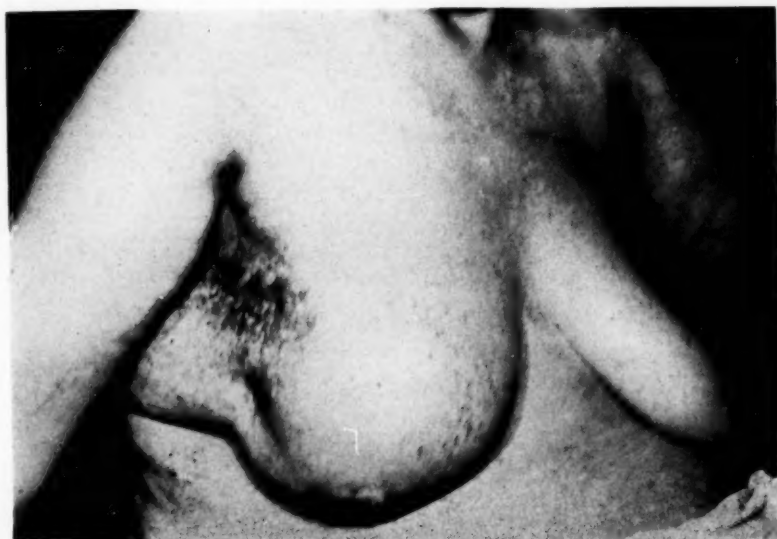
FIG. 1.—R. S. Showing the carcinoma of the right breast which has been heavily treated by interstitial and external irradiation for a period of six years, four months.

chromatic and look atrophic but capable of activity." The breast mass seems to be entirely inactivated clinically. It has not seemed necessary to give more treatment since June, 1928, three years ago. There is no evidence of metastasis. Patient is in splendid general health, six years, four months, since commencing her irradiation régime, of both interstitial and external therapy.

CASE II.—M. Z., female, aged sixty-two years, came to the Memorial Hospital, August 18, 1924, stating that she had a lump in the right breast the size of a walnut that had been present for four months. In the upper outer quadrant of the right breast was a hard mass 3 by 2 by 2 centimetres. The clinical diagnosis of cancer was made, and treatment instigated. Chest plate is negative. The patient has a serious cardiac condition which contraindicates any operative procedure. Her treatment consisted of: Platinum radon needles inserted into the breast tumor for a total of 1,485 millicurie hours. Radium tray 2,800 millicurie hours over the lesion. Gold radon seeds into the axilla for 943.2 millicurie hours. Four low-voltage X-ray treatments. Eight high-voltage X-ray treatments.

On March 20, 1931, a Hoffman punch biopsy was taken which showed the presence of carcinoma. Clinically there is a dense fibrotic mass that seems inactivated; and the

patient has received no treatment for the past three years. It is now six and one-half years since treatment was first begun.

CASE III.—L. M., married female of fifty-one years entered the Breast Clinic of the Memorial Hospital, March 20, 1925. Since fourteen years of age has had a lump in the right breast. (See Fig. 2.) Has begun to grow and now measures 2.5 by 2.5 by 1.5 centimetres. There is suggestion of skin fixity. The mass is situated toward the tail of the right breast. X-ray of chest was negative for metastasis. The treatment consisted of the following: March, 1925, a high-voltage X-ray cycle of four treatments was given over the breast, axilla and supraclavicular space. August, 1928, two high-voltage X-ray treatments were given over the breast. January, 1929, two high-voltage X-ray treatments were given over the axilla and supraclavicular region. January, 1929, two radium packs, totaling 14,000 millicurie hours, were applied over the breast tumor. April, 1929, two radium packs, totaling 16,000 millicurie hours, were again applied over the breast tumor.

During March, 1931 (six years since entering the clinic), a Hoffman punch biopsy was made and the tissue revealed cancer present. The patient died in September, 1931,
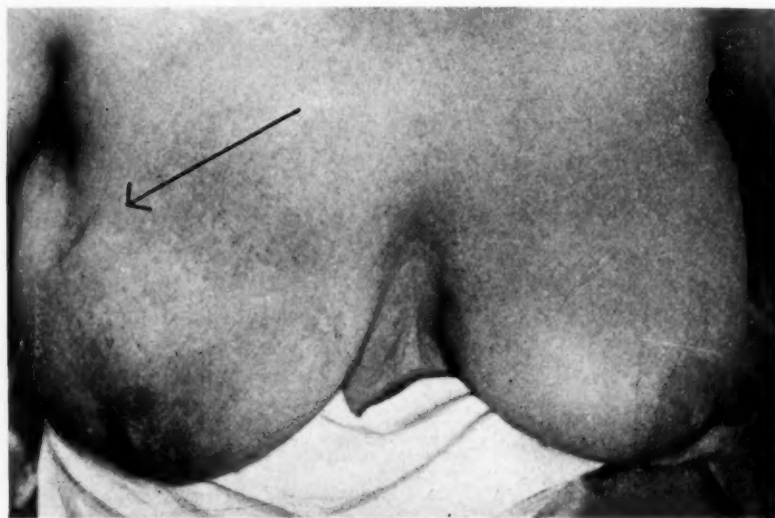
FIG. 2.—L. M. The arrow points to the cancer of the right breast.

of a stroke of apoplexy, her cancer having been under control, even though present, for a period of six and one-half years by external irradiation alone.

Statistical Studies.—The study herein reported is based on a survey of 199 *operable* cases treated at the Memorial Hospital during the decade January 1, 1916, to January 1, 1926. This group by no means represents the total number of operable cases that came to the clinic during those ten years. It does, however, represent all the operable cases on which full and complete data are available. Each case reported has had a microscopical study made of the tissue, so that there is no question as to the exact nature of the neoplasm.

It is a great pity that many of our operable cases (not included in this report) treated by irradiation alone have had to be excluded because of the fact that no microscopical studies were made. Complete information on this group is especially desired. However, this was deliberately done at the

time, following out the suggestion of Ewing that a larger number of operable cases treated by irradiation only would survive the five-year period if *no* biopsy were taken at first. The procedure of cutting directly into the tumor opened many lymphatics and blood-vessels for the free entrance and dissemination of the cancer cells. With the new method of biopsy by aspiration and small punch, the latter wound of which is immediately electro-desiccated, the danger of dissemination is minimized. Today we obtain a microscopical report in nearly every case. Many of the operable cases treated by only irradiation methods have gone on to a "five-year cure"; but inasmuch as there is no microscopical study made on these cases, this group is eliminated from consideration as but few would have the generosity to accept the report.

Likewise, there is a group of operable cases treated by irradiation methods only that have died of unquestioned clinical carcinoma—but as there was no microscopical study, they are similarly excluded from this study. The latter two groups are not herein reported as it would be obviously unfair to report the one group without the other. We repeat that this study is strictly confined to those cases regarding whom complete data are available for a period longer than five years.

To facilitate this study, the 199 cases are grouped into four series, as follows:

Table I

Series A

115 Cases—Either Dead or Lost

	Cases
Treatment by surgery (only)	18
Treatment by irradiation (only)	21
Treatment by combined irradiation and surgery	76
Total	115

Of these 115 cases, we know that at least six lived five years or more.

Series B

66 Cases—All Now Living Over Five Years

	Cases
Treatment by surgery (only)	2
Treatment by irradiation (only)	12
Treatment by combined irradiation and surgery	52
Total	66

Series C

16 Cases—Dead of Intercurrent Disease

	Cases
Treatment by surgery (only)	3
Treatment by irradiation (only)	4
Treatment by combined irradiation and surgery	9
Total	16

Of these sixteen patients, nine lived more than five years.

Series D

2 Cases—Very Young Subjects Living Without Disease

Cases

Treatment by surgery (alone) 0
Treatment by irradiation (alone) 0
Treatment by combined irradiation and surgery 2

Total 2

No case in the above series A, B, C, and D, has been studied for less than five years; some have been followed as long as twelve years.

Series A.—Series A comprises those 115 patients either known to be dead or about whom we have been unsuccessful in our efforts to obtain any information. For the purpose of these studies we assume that the lost cases are dead. We realize that there are probably some who are cured but cannot prove it. Eighteen patients (15.5 per cent.) of Series A were treated by surgical methods only, without irradiation being employed as an adjunct.

When it is stated that a case was treated by "irradiation only," it is meant that the attempt *to cure* has been by the employment of one or more of the irradiation methods. Up to the present but little success has attended the attempt to cure mammary cancer by the application of *external irradiation* by X-rays and radium packs. Unquestionably, there is an occasional case cured by external irradiation, but that method cannot be relied on with our present technic for the cure of such a normally radioresistant tumor. On the other hand, we are testing the combined use of *interstitial* (insertion of radon into the tumor and surrounding areas) *and external* irradiation. In order to cure a radioresistant cancer such as the fibrocarcinoma, it is often necessary to give such large quantities of interstitial and external irradiation that marked skin damage results and a simple mastectomy becomes necessary. Or it may be necessary to employ surgery for the *late* effects of irradiation of the skin. In either instance, the patient is still considered to remain in the irradiation group. We regard such a case as one that is being treated by irradiation methods, but that it is necessary to employ a surgical procedure to treat the irradiation complication. Should this same patient *not* survive a five-year cure, the failure is charged against irradiation methods and *not* against surgical methods. On the other hand, if treatment has resulted in a five-year cure, the success is accredited to irradiation. In other words, the success or failure of the treatment is attributed to that method along which the original line of therapy was laid down. There were twenty-one patients (18 per cent.) treated by irradiation alone in Series A.

By the combined irradiation and surgery method we mean that the patient is first treated by a pre-operative high-voltage X-ray cycle consisting of two treatments over the breast tumor and one each over the axilla and the supraclavicular space. Approximately a month following the last of these four treatments the radical amputation is performed; one month later the post-operative X-ray cycle is begun over the operative area, the axilla and the supraclavicular space. Unless the post-operative treatments are given within

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eight to ten weeks following the operation, it should not be properly considered a "post-operative cycle."

It occasionally happens that one believes himself to be dealing with a benign lesion only to find at the operating table that it is a malignant tumor. This tumor has received no pre-operative irradiation but following the operation the patient receives the post-operative irradiation and hence is still considered to be in the group of combined irradiation and surgical treatment. Furthermore, if interstitial irradiation is employed instead of or accompanied by external irradiation, and surgery is later employed, the case is considered to be in the group of *combined irradiation and surgery*. In Series A, there were seventy-six cases (66 per cent.) treated by the combined method.

Series B.—Series B is composed of sixty-six living patients, no one of whom has been treated or observed for a period of less than five years. In Memorial Hospital it is but the rare case treated by surgery only. Those thus treated are usually not deliberately so done but they represent instances of difficult or frankly mistaken diagnosis. In Series B there are only two such cases (3 per cent.). There are twelve cases, or 18 per cent., of Series B treated by irradiation methods only; and fifty-two cases (79 per cent.) treated by the combined irradiation and surgical method.

Series C.—Series C comprises sixteen patients, of whom twelve died of some intercurrent disease, while four could not be traced. The reason for this large number of deaths from diseases other than cancer is the advanced age of the patients. Seven of the sixteen patients were very old, their ages being respectively ninety, eighty-five, eighty-four, seventy-nine, seventy, seventy, and sixty-nine years. The deaths were chiefly from heart disease and pneumonia, the terminal disease groups so prevalent at these advanced ages. All but four either died or were lost without clinical evidence of cancer. The four patients (25 per cent.) who died of intercurrent disease having clinical cancer present, were aged eighty-five, seventy-nine, sixty-nine and ninety years respectively. In no one of these four patients was cancer an important contributing cause of death. Nor was it considered to be particularly menacing in any of these elderly patients. In Series C, surgery alone was employed in three patients (19 per cent.), irradiation alone in four (25 per cent.) and combined irradiation and surgery in nine patients (56 per cent.).

In elderly people it is commonly a question of fine judgment as to the best type of management. If the patient is aged seventy-five years or older, the best procedure is to disturb the patient as little as possible. If there is an impending ulceration of the overlying integument, it is better to entirely withhold irradiation. If no ulceration is imminent, only *divided* irradiation doses should be employed. In the older people even the excoriation of the skin should be carefully avoided as they do not well withstand the pain of the irradiation burn; nor do they well endure the gastro-intestinal upset of irradiation. One hopes to avoid a breaking down of the tumor. If the aged patient has a tumor present which is commencing to ulcerate, it is often best

to perform a simple and quick mastectomy *under novocaine* anæsthesia and promptly get them out of bed following their operation. With a little assistance from irradiation or the simplest type of surgery, the patient will frequently go on for years without distressing symptoms from metastasis, and may then die from an intercurrent disease. Of the sixteen cases of Series C, nine are five-year successes. Seven died of intercurrent disease before the five-year period was up, but not one of the sixteen cases died of *cancer*. Four patients did, however, have cancer *present* at the time of death. In the elderly cancer patient, judicious management is all important.

Series D.—Series D is composed of two cases only. It is a rare and interesting group in which we are dealing with cancer of the breast in the *very young* subject. One patient was aged seventeen years and the other aged nineteen years. Both patients had cancer present. They would be included in cancer statistics as cures. Doctor Ewing, our pathologist, diagnosed each specimen as "carcinoma" but qualified his diagnosis by stating that "although each is microscopically malignant, the case is clinically benign." This opinion he based on the rarity of the areas where infiltration and invasion had occurred; and on the fact that the lesion is sharply circumscribed and thoroughly encapsulated. Some of the ducts were filled with definite cancer tissue while other ducts retained their normal or adenomatous form. It is a very localized cancer process. Sir Lenthal Cheatle considers this group as definitely carcinomatous, while Ewing, on the contrary, considers the process benign on account of the youthfulness of the patient, the encapsulation, and the fact that the process is only beginning to invade the basement membrane.

These two cases are being excluded from our true cancer series for the above reasons. After deducting them from the 199 original cases, the number in our study is reduced to 197.

Both of these young patients were treated by a local removal of the tumor, followed by implantation of radium in and about the wound, and this was later followed up by the employment of radium packs and high-voltage X-ray over the local and drainage areas. Both patients are free of disease, one for seven years, three months, and the other seven years.

The following table (Table II) shows the proportion of the methods of treatment employed in relation to the 197 cases:

TABLE II
197 Patients Treated Five Years or More

Series	Irradiation (only)	Surgery (only)	Combined surgery and irradiation
	Cases	Cases	Cases
A	21	18	76
B	12	2	52
C	4	3	9
Totals..........	37 (19%)	23 (11.7%)	137 (69%)

Ninety-one of the 197 cases lived five years or more, this being 46 per cent of our total series. Table III presents these according to group and number of years lived:

TABLE III

Lived Five Years or More

Years	5	6	7	8	9	10	11	12
Series A 115 cases	16	9	1	1	0	1	0	0
Series B 66 cases	66	15	6	8	6	8 (12%)	1	3 (5%)
Series C 16 cases	9	2	0	1	0	0	0	0
Total	91							

Total, ninety-one cases (out of 197 cases) = 46 per cent.

The next table (Table IV) gives the method of treatment and the results of each method in the series of 197 cases.

TABLE IV

Treatment Results Five Years

	No.	Died other disease	Basis of calcu-lation	Num-ber living	Per cent living	Died of cancer	Per cent	Living with disease	Per cent	Living without disease	Per cent
Surgery (alone)	23	3	20	2	10	18	90	0	0	2	10
Irradiation (alone)	37	4	33	12	36.3	21	63.3	4	12.1	8	24.2
Combined surgery and ir-radiation	137	9	128	52	40.6	85	66.4	3	2.3	49	38.2

The basis of calculation was arrived at by deducting from the total number of cases treated by the respective methods the number who died of intercurrent disease. Those cases treated by surgery alone in this series seem to be particularly unfortunate, as there were only 10 per cent. of them living at the end of five years. There were thirty-seven cases treated by irradiation alone; four died of intercurrent disease; twelve are living, making 36.3 per cent.; four are living with disease; and eight, or 24.2 per cent., are living without disease. *The important point of this group is that 36.3 per cent. treated by irradiation methods alone are* LIVING *over five years.* The fact that four patients of these twelve have disease present is probably not nearly so important since irradiation is the method of therapy being employed. *Of those treated by a combined surgical and radiation method, fifty-two (40.6 per cent.) have lived over five years.* Three of these patients have disease present

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and forty-nine patients (38.2 per cent.) have no clinical evidence of disease. In other words, the five-year result by irradiation treatment (36.3 per cent.) is interesting when compared with the combined surgical and radiation method (40.6 per cent.). This figure, 36.3 per cent., is an important one for the general medical man to know because it lends more than a ray of hope for the operable case in whom operation is contraindicated by the presence of other diseases. The likelihood of a five-year cure by radiological methods approaches those results obtained by the radical amputation and radiation treatment combined.

It is of further interest to note that there is a marked difference between those patients treated by the combined method (38.2 per cent.) and the irradiation method (24.2 per cent.) as concerning the presence of disease. However, I believe the 24.2 per cent. is low because the patients may have the disease present and still have the carcinoma inactivated and the process completely stopped. It will require observations covering a period of ten or twelve years to settle the relative long-run value of these two methods.

Doctor Lee,[5] three years ago in a survey of five-year results at the Memorial Hospital, after studying the relative value of pre-operative irradiation and post-operative irradiation, came to the following conclusion:

TABLE V

Results in Primary Operable Patients

	No.	Alive well	Alive recurrent	Dead	Dead of intercurrent disease	Lost track	Per cent five-year results
A Pre-operative irradiation, surgery, post-operative irradiation	41	14	1	24	3 (after five years)	0	39
B Surgery, post-operative irradiation	76	25	0	49	0	1	35
C Irradiation	45	11	1	22	6 (after five years)	5	36

In Doctor Lee's study of the 162 operable cases mentioned in Table V, there is a 4 per cent. better result in those forty-one cases having the advantage of pre-operative irradiation over those who had only the post-operative irradiation. In my series of 128 cases, the combined method gives 40.6 per cent. five-year cures, which is 1.6 per cent higher than the series reported by Lee. This may possibly be explained by the fact that in my series, which is more recent, a larger proportion were treated by the *high-voltage* X-rays, rather than the low-voltage.

It is interesting, also, that Doctor Lee's studies of those cases treated by

irradiation methods only are almost identical with mine (36 per cent. and 36.3 per cent. respectively).

Biopsy.—Mention must here be made of the newer methods of obtaining biopsy material in those cases where diagnosis is difficult. Even in the hands of those clinicians who possess a large experience in the diagnosis of breast lesions, there will always remain a group which is clinically impossible to diagnose. The aspiration biopsy methods of Guthrie,[6] ot Martin and Ellis,[7] and the punch technic by Hoffman[8] add greatly to the ease of diagnosis in this difficult group. Incidentally, the surgical technic is quite simple. The *important factor* is the pathologist, who should possess a large experience in the interpretation of such pathological material. By the use of these methods one may have a microscopical diagnosis within ten minutes. Valuable time will be saved; the patient will be spared a bigger biopsy procedure, and the danger of the usual biopsy will be minimized.

RÉSUMÉ

(1) A study is made of 199 primary operable cases of mammary carcinoma on whom complete data for a period of no less than five years are available.

(2) On account of the importance of the debilitating diseases other than cancer, which diseases contraindicate radical surgical procedures, special examination is made of those cases which were treated by irradiation methods.

(3) Standard radical mastectomy in the good general hospitals of America yield from 32 to 39 per cent. five-year cures.

(4) The author's criteria of operability are discussed.

(5) Obtaining a "five-year cure" by irradiation methods is accomplished along totally different lines than that by a surgical procedure. The latter is by a wide extirpation of the breast, its contiguous structures and its drainage basin, while the irradiation "cures" are produced by locking up the local disease in dense fibrous tissue, and starving the disease process by endarteritis, and the direct insult to the cancer cell which is produced by the rays.

(6) It is believed that external irradiation alone by radium packs and high-voltage X-rays is, as a rule, not sufficiently potent therapy to effect cures in mammary cancer. We consider breast carcinoma to be a relatively radioresistant form of cancer.

(7) Most cases of "cures" by irradiation have been accomplished by the combined interstitial insertion of radium together with external radium packs and high-voltage X-rays.

(8) Of the thirty-seven cases treated by irradiation methods only, four died of intercurrent disease, twenty-one died of cancer, and twelve, or 36.3 per cent., are living over five years.

(9) Of the 137 cases treated by the *combined* irradiation and surgical method, nine died of intercurrent disease, eighty-five died of cancer and fifty-two, or 40.6 per cent., are living over five years.

(10) These improved results (40.6 per cent.) we rightly or wrongly deem to be due to the added factor of irradiation.

CONCLUSIONS.—Irradiation, if properly applied, can be relied on to effect a "cure" in cases of mammary cancer, in 36.3 per cent. It offers a substitute weapon but slightly less effective in five-year results than the combination of irradiation and surgery (40.6 per cent.). In cases where surgery is contra-indicated the combined interstitial and external irradiation is our most efficient agent.

BIBLIOGRAPHY

[1] Adair, Frank E.: The Response of Various Types of Breast Cancer to Radiation. Radiology, vol. xiii, p. 319, October, 1929.

[2] White, William C.: Cancer of the Breast. Harper & Bros., p. 24, 1930.

[3] Lee, B. J., and Tannenbaum, N. E.: Inflammatory Carcinoma of the Breast. Surg., Gynec., and Obstet., p. 580, November, 1924.

[4] Ewing, James: Radiosensitivity. Radiology, vol. xiii, p. 313, October, 1929.

[5] Lee, Burton J.: The Therapeutic Value of Irradiation in the Treatment of Mammary Cancer. ANNALS OF SURGERY, pp. 26–47, July, 1928.

[6] Guthrie, C. G.: Gland Puncture as a Diagnostic Procedure. Bull. Johns Hopkins Hosp., vol. xxxii, p. 266, 1921.

[7] Martin, Hayes E., and Ellis, Edward B.: Biopsy by Needle Puncture and Aspiration. ANNALS OF SURGERY, p. 169, February, 1930.

[8] Hoffman, William J.: New Technic and Instrument for Obtaining Biopsy Specimens. Amer. Jour. Cancer, vol. xv, No. I, January, 1931.

STEREOSCOPIC RÖNTGENOGRAPHY OF THE BREASTS

AN AID IN ESTABLISHING THE DIAGNOSIS OF MASTITIS AND CARCINOMA

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CLINICAL evidence is often inconclusive concerning the character of an abnormal mass palpated within a breast of a patient at the cancer age. The differentiation of a chronic mastitis from early carcinoma, especially of the scirrhus form may be most puzzling or impossible. It is the recognition of this fact which has led investigators to seek other means for this early differentiation such as transillumination by Cutler (1929)[1] and radiography by Warren (1930).[2]

The latter method consists in taking stereoscopic röntgenograms employing a technic to bring out detail of the soft tissue of the breast, the subpectoral muscles, the axillary fossa, and adjacent ribs. We wish to emphasize certain differential characteristics between chronic mastitis and early carcinoma which have been found reliable after further experience with this method of examination.

Cutler has found that transillumination has certain definite limitations. These are in part of a mechanical or physical nature. In the large nonpendulous breast closely applied to the chest wall, it was found impossible to place the lesion between the source of light and the eye of the observer, and there was a real danger of missing small solid tumors located near the surface of the breast due to the diffusion of light. Of greater importance than these which permit correction or improvement in technic is his finding that it was impossible to differentiate between a benign and malignant tumor of the breast even under optimum working conditions.

In carrying out our work, the röntgenological examination appears to us to have the following advantages over transillumination. (1) It is possible to determine encapsulation of tumor. (2) Transillumination permits no analysis of structure within a mass while it is this analysis by röntgenological examination which permits the differentiation between chronic mastitis and malignancy. It is this differentiation which constitutes the chief confusion clinically. (3) Transillumination gives no information concerning deeper structures while the röntgenological examination gives data concerning the involvement of the pectoral muscles, ribs, and axillæ. It is this kind of evidence (of metastatic invasion) which determines the type and course of treatment. (4) By transillumination it is not possible to recognize such changes as calcification which is readily determined by röntgenography. (5) Röntgenological examination has the advantage of stereoscopy. (6) It also constitutes a permanent record permitting future comparison by
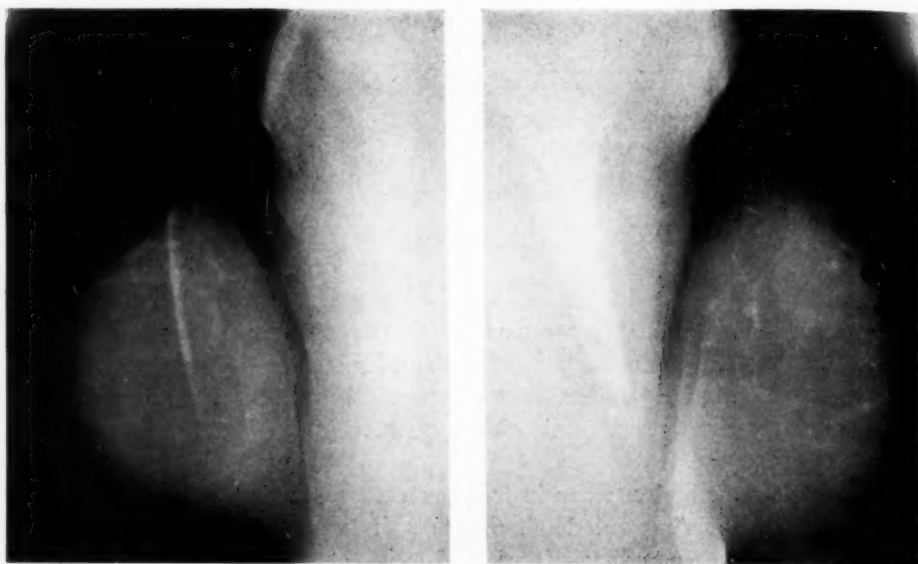
FIG. 1.—Normal obese breasts. R. H., married, forty-one years of age, and without significant history relative to breasts. While these breasts are large and heavy, their physical size does not change the general röntgenological appearance of the normal breast. The presence of a large amount of fat, permits sharp definition of breast pattern, particularly of the fibrous septa of the breast. The band of increased density crossing the right breast represents a part of the patient's clothing.
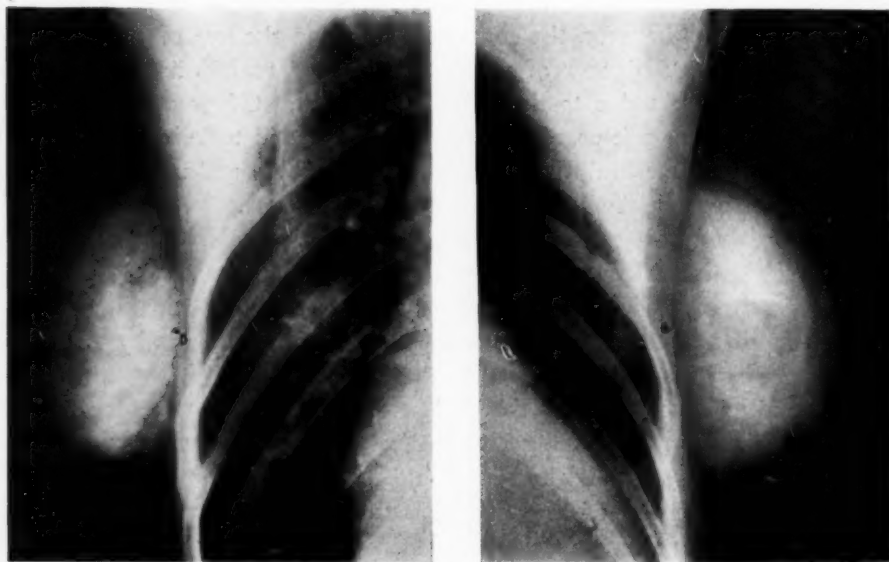
FIG. 2.—Diffuse mastitis of both breasts with cysts. E. M., housewife of fifty-eight years, has a history not pertinent to breasts and a physical examination of the breasts was reported negative. Röntgenological examination showed numerous compact masses (A) resembling cysts. Note the lobular appearance of these masses, their smooth margins, and the absence of infiltration and skin involvement. Base (B) of the breast is free; no evidence of metastases. In spite of the extensive pathology of these breasts, the clinical examination failed to detect any changes.

serial röntgenographical study and in this regard is of help in establishing the prognosis during the course of irradiation or other treatment.

Fig. 1 illustrates the normal breast structure of an obese individual. The presence of a large amount of fat in a heavy breast constitutes a definite handicap in the identification of masses by physical examination. The physical size of the breasts, however, does not prevent a satisfactory radiographical examination; in fact, the presence of fat serves as a tissue of contrasting density which permits the delineation of opaque masses within such breasts.

In working out the differentiation of mastitis and carcinoma, it is well to carry the gross pathological picture in mind. Mastitis in the true sense is an inflammatory reaction in either the acute or chronic state. Often both
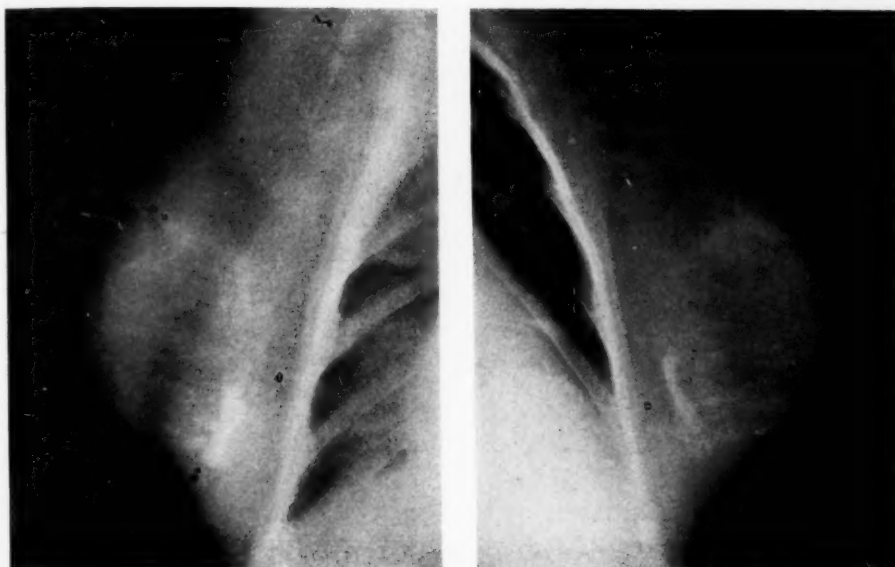
FIG. 3.—Acute and chronic mastitis in an obese breast. Patient was a virgin of fifty-eight years, with a two months' history of transient recurring pain in both breasts. Physical examination demonstrated the presence of tender masses within the breasts. There was no discharge from the nipples. Films show an old coarse fibrosis (C) with superimposed soft, acute changes (B). Note that in acute mastitis the glands of the axilla (A) may be considerably enlarged. The preservation of the breast pattern and absence of pectoral involvement at (D) is against carcinoma.

stages are present together. In the gross cross-section, one can visualize the course of histological changes which ensue: Œdema with associated swelling or distortion of structures; infiltration of cells; beginning repair; contraction and scarring; the obstruction of a duct or part of an acinus with dilatation and formation of a cyst; often a certain amount of hyperplasia and thickening of the glandular tissues which is thought at times to result in the formation of a malignant condition.

The gross structure of the breast with the denser duct and glandular structures interspersed among the fat lobules (which are more radiotranslucent) is such as to show these pathological changes in much the same fashion as inflammatory changes show up in the lungs. Acute changes are

soft, feathery, indistinct, and diffuse, while the more chronic changes are dense, sharp, distinct, and more compact due to the connective tissue changes. Both acute and chronic changes may occur side by side with all gradations between. Cysts are identified from fat lobules by their greater density and sharp outline, usually occurring in the region of the ducts. Cellular masses are much denser, their density depending on the type of cell. Through all these changes a definite architectural pattern typical of the breast can be made out.

The gross appearance on cut-section of carcinoma is characterized by a hard, dense tumor infiltrating the normal structures in all directions. This
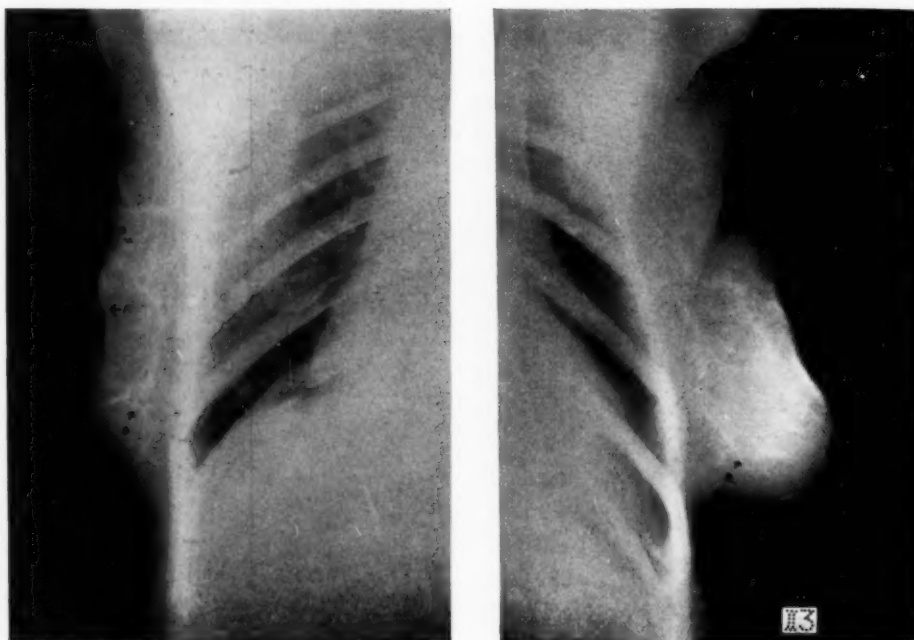
Fig. 4.—Chronic mastitis with cysts. A. F., married woman of forty-four years, gave a history of removal of "tumors" from breasts fifteen years before admission. Biopsy report stated that masses were benign according to patient's statement. Physical examination revealed palpable mass, irregular in outline in right breast. Films of breasts showed a very diffuse process with much fibrosis (B) due to mastitis with cyst formation. The right breast is deformed by a scar (A) of old operation. This case has been followed two years without evidence of malignancy.

is accompanied by an extensive connective tissue reaction with a tremendous shrinkage and distortion of local structures which have been infiltrated. This is noted even in small tumors when examined pathologically.

This tumor mass presents essentially the same picture when examined by stereoscopic röntgenograms. A compact mass with indefinite periphery due to the infiltrating invasive tumor and a dense connective tissue reaction is noted which displaces and deforms the normal architecture of the breast.

Contrasting these two röntgenological pictures (mastitis and carcinoma) the following differential features are to be noted.

(a) Carcinoma finds its origin in a single area or focus within one

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breast. (Fig. 5.) In mastitis, on the other hand, there are characteristically multiple points of origin and often both breasts are involved. Early carcinoma is practically never found in both breasts simultaneously, and even later, when involvement of both breasts may occur, the original tumor is larger than the metastasis and at this late stage metastatic invasion along lymph channels is clearly evident on the most cursory perusal of the films.

(b) Carcinoma forms a compact mass with an indefinite periphery (Figs. 5 and 6) while mastitis produces a very diffuse mass (Figs. 2, 3, and 4) which shades off imperceptibly to the normal structures peripherally.

(c) Scarring (reparative fibrosis), (Figs. 3 and 4), which is so common
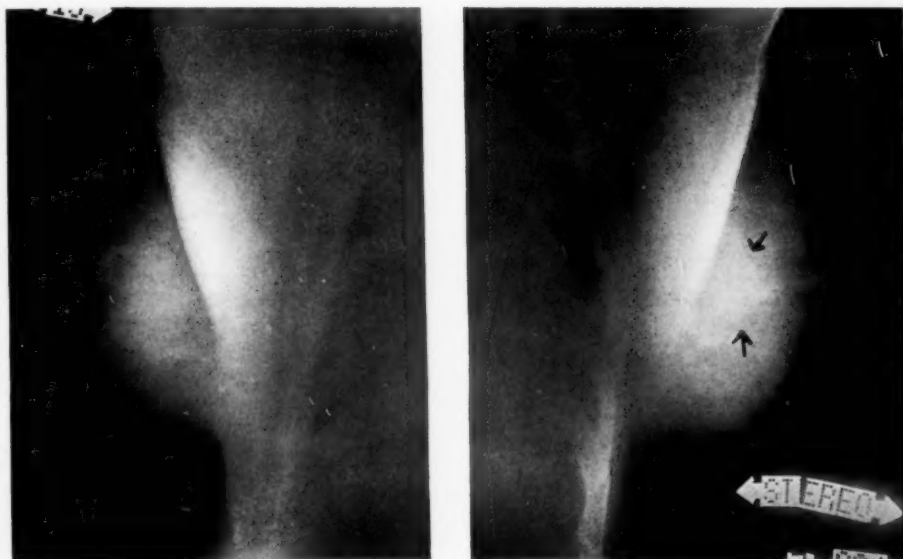
Fig. 5.—Early carcinoma of left breast. L. D., single woman of fifty-four years, first felt lump four years ago in left breast; no discharge from nipples. There is history of artificial meno-pause nine years ago. Röntgenological examination showed right breast normal. The left breast showed a small area of dense tissue with irregular margins in upper portion of the breast. A very early carcinoma was considered likely in view of the character of the mass. The axillary regions are not well seen. The clinical diagnosis was chronic cystic mastitis. However, at operation a short time later, radical breast operation was done because of the appearance of the cut section of the mass (thought to be early carcinoma). *Pathological report.*—Mass the size of a walnut, gray in color, irregular in outline, with numerous strands extending out into surrounding tissue. Micro-scopic section showed scirrhous carcinoma. Intensive radiation given for several years; no evidence of recurrence during course of four years following operation. Note the irregular border of mass and its single character. Its early status is reflected not only by its small size but in the absence of macroscopic involvement of pectoral muscles.

in chronic mastitis, results in no massive distortion of the normal breast architecture. The scarring (infiltrating fibrosis) of malignancy (Fig. 6) grossly distorts this architectural breast pattern. This is especially true of the scirrhous type.

(d) The thin septum between the breast structure and the pectoral muscles is never destroyed in mastitis (Figs. 2 and 3) while in carcinoma (Fig. 6) invasion often results in its destruction at the site of the mass.

(e) The presence of large nodes (Fig. 6) and other metastases serve to identify a late carcinoma of the breast.

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At times it is possible to obtain clues concerning the type of breast malignancy. Thus (a) a scirrhus carcinoma produces much more distortion of the breast pattern than a medullary carcinoma. (b) The latter often produce considerable bulk resulting in a marked disproportion in the size of the breasts. (c) Serial films demonstrate the more rapid growth of the medullary type. (d) Early evidence of local metastases is common in this latter type. It is frequently noted, however, that malignant tumors may show all degrees of variation from a predominant sclerosis to one with very little connective tissue reaction and classification into types before operation becomes impossible or hazardous.

Mastitis is an extremely common lesion. A certain amount of scarring as a result of inflammatory reaction is present in many women (in both nulliparous and multiparous women). The degree of involvement varies tremendously and seems to bear no relation to the size or shape of breasts, age of patient after full development of breast, or the number of lactation periods. Lactation may leave few scars or other changes while a middle-aged woman with no clinical history of inflammatory changes at lactation occasionally shows most marked changes in the density of the periglandular or ductular portions of the breast. In the identification of this lesion, changes due to menstruation, lactation, atrophy, shrinkage due to loss of weight, and changes due to involution must all be borne in mind as complicating factors.

With proper precautions and careful follow-up, a diagnostic precision of considerable accuracy can be obtained. It is often impossible to identify or rule out an early scirrhous carcinoma in the gross section when it is enmeshed in a dense area of mastitis. Microscopical study often is necessary to prove its presence or absence. In the case of very small tumors (5 to 10 millimetres in diameter) which are buried in a mass of inflammatory change, the identification of the tumor may be impossible with the present technic. Repeated examination, however, should reveal the tumor before the diagnosis can be established by clinical means. Present-day practice is of course to perform a mastectomy if there is a possibility of malignancy being present. This method of serial röntgenographical study should open up a new means of following all cases in which the evidence is insufficient to justify operation but where the exact diagnosis remains doubtful.

As regards results, correct diagnoses have been made in 85 to 90 per cent. of cases coming to operation. This work was done as a routine procedure without knowledge of the final diagnosis. Of the group having palpable breast masses classified by means of this method as mastitis, and eliminated from the malignant group, none have developed a malignant tumor during approximately four years of observation. To extend the experience and accuracy of the röntgenologist, it is most important to secure the cooperation of the surgeon and pathologist in order that every breast examined can be followed up. Films of the specimens removed at operation should

be taken. The gross specimen should be examined with the pathologist comparing its pathological picture with the röntgenological densities.

Aside from the value of this method as an aid to diagnosis, the röntgenographical examination can play an important part in establishing the prognosis. The extent of the tumor can be traced out and the manner of its spread through the base along the lymphatics through the pectoral and axillary lymph-nodes or through to the pleura can be established. Involvement of these channels is of extreme importance in determining the feasibility of mastectomy with block dissection. The recognition of extension into the pleura changes the prognosis of a case, which from the clinical viewpoint with no other evidence of metastases appeared favorable for opera-
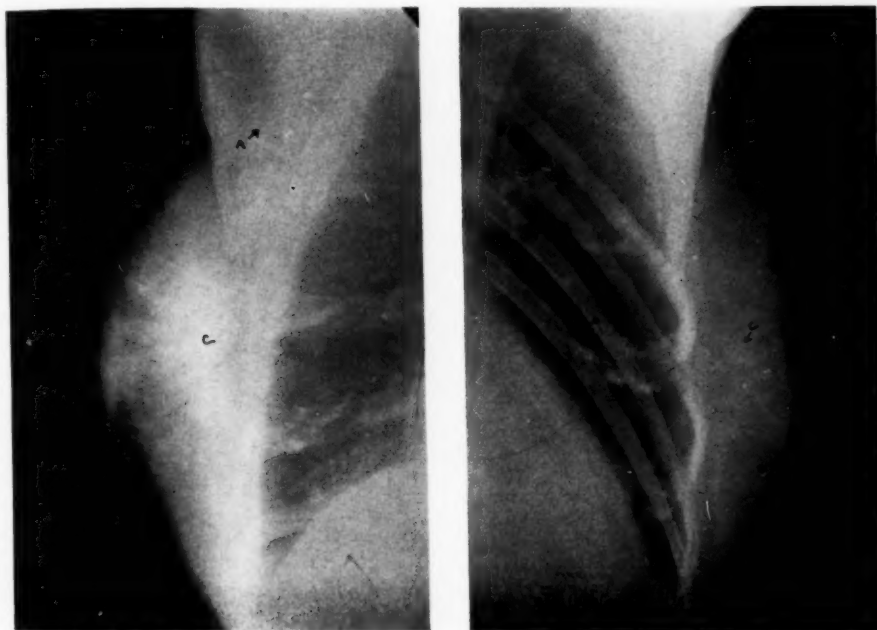
FIG. 6.—Advanced breast carcinoma. C. A., housewife of fifty-six years, gave a history of a mass in the right breast, first noted two years before admission. This was followed by similar involvement of left breast. Physical examination showed visible and palpable tumors of both breasts. Röntgenological examination showed adeno-carcinoma of breasts with ulceration and invasion of pectoral muscles and axillæ. Films of spine showed evidence of metastatic invasion with collapse of fifth cervical vertebra. Under deep therapy the masses in the breast decreased in size. Also, some repair occurred in the collapsed cervical body. Note absence of septum between base of mammory gland and pectoral muscles as well as masses (C) within breasts and dense infiltration at skin surface (B). There is a large node in the right axilla at (A).

tion, to an unfavorable one. It is unusual for the axillary nodes to be involved without some evidence of the spread being obtained from the films. The extent of this involvement should be known to the surgeon so that he may include an area well beyond it in the dissection. Many tumors recur because the surgeon is unable to determine accurately the exact extent of the metastatic invasion at the time of the operation, and any method which will fortify him and impart to him the extent of his task will aid the patient and surgeon alike.

Summary.—The differential diagnostic röntgenographical features of mastitis and carcinoma which have been found helpful in this clinic are discussed. It is believed that this method imparts information not obtainable by other means known at the present time. Besides its diagnostic value, the method is of definite aid in establishing the prognosis before treatment and subsequent serial röntgenographical study will give important information concerning the response to treatment (as irradiation, *etc.*). It may not be amiss to add that this method is not offered as a substitute for or to replace any portion of the physical or other examination. The physical examination of the breast cannot be too exactly carried out. The röntgenographical examination should serve, however, as a valuable supplement in establishing both the diagnosis and prognosis.

CONCLUSIONS.—(1) Most of the gross pathological changes in the breast are as readily identified in stereoscopic röntgenograms as they are in the gross specimen at biopsy or autospy.

(2) Stereoscopic röntgenograms of the human breast offer many advantages in establishing the diagnosis in suspected cases of malignancy, not obtainable by clinical methods.

(3) The earliest changes due to scirrhous carcinoma in the presence of a chronic mastitis are as difficult to identify as they are in the gross specimen.

(4) In addition to the diagnostic aid which this method offers, valuable information can be obtained concerning the prognosis before treatment.

(5) Serial study is of great importance in following doubtful cases and cases under irradiation treatment.

(6) Coöperation between the surgeon and the radiologist is essential if the diagnostic accuracy is to be maintained at a high level.

BIBLIOGRAPHY

Cutler, Max: Transillumination as an Aid in the Diagnosis of Breast Lesions. Surg., Gynec., and Obstet., vol. xlviii, p. 721, 1929.

Warren, S. L.: Röntgenological Study of the Breast. Amer. Jour. Rönt., vol. xxiv, p. 113, 1930.

SARCOMA OF THE BREAST

A REPORT OF SEVEN CASES

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Sarcoma of the breast is a rare disease, as is shown by examination of the records of all tumor cases admitted to the State Institute for the Study of Malignant Disease. From 1913 to November 1, 1931, there was a total of 11,490 tumor cases, 9,540 of which were malignancies. Of the total number of malignancies, 8,703 were of epithelial origin, and 749, or 7.8 per cent., were of connective-tissue origin or sarcoma, and eighty-eight leukemias. Of the 749 sarcomas, only seven, or 0.9 per cent., were in the breast; of the 1,395 malignancies of the breast, only 0.5 per cent. proved to be sarcoma. Of 1,837 breast lesions, 75 per cent. were carcinomas, 0.38 per cent. sarcomas, 22 per cent. benign tumors and cysts, 1.2 per cent. inflammatory lesions, and 0.38 per cent. tuberculosis. There were 1.383 carcinomas, including sixteen Paget's disease, two epitheliomas of the skin of the breast, three nævus-cell carcinomas of the skin, seven sarcomas, 407 benign tumors and cysts, twenty-three inflammatory lesions, seven tuberculosis, four anomalies, and one traumatic lesion.

D'Aunoy and Wright,[1] in 1930, collected the reported cases of sarcoma of the breast since the tabulation by Geist and Wilensky[2] in 1915. These figures, together with our seven cases, bring the total to 510.

Deaver and McFarland,[3] in 1917, made a rather exhaustive study of the literature and tried to classify the types of growth from the histories and data given, but confessed that it was extremely difficult to do so. They called attention to the fact that the generation of surgeons and pathologists in the last half of the nineteenth century reported a great many more cases of sarcoma of the breast than the present generation. They suggested that this may be due to the present refinements in histological diagnosis.

These tumors begin as isolated, rounded or lobulated nodules; solid and cystic tumors are also observed. The cystic forms produce exceedingly large tumors as are shown in Figs. 1, 2, and 3.

Ewing[4] calls attention to the fact that if many of the tumors that are called adeno-sarcoma and sarcocarcinoma were eliminated, there would be fewer cases of true sarcoma of the breast. The types of sarcoma described are round-cell, spindle-cell, adeno-sarcoma, mixed tumors showing fibrosarcoma, myxosarcoma and osteosarcoma. Quoting Gross, Schmidt and Schuoler, he states that adeno-sarcoma forms about 7 to 10 per cent. of the breast neoplasms; that adeno-sarcoma represents the malignant form of adeno-fibroma, but that adeno-sarcoma when recurring often produces pure spindle-cell sarcoma. "In the early stages, the tumors are circumscribed or encapsulated, but active growth leads to dissemination through the organ, and fungating masses perforate nipple and

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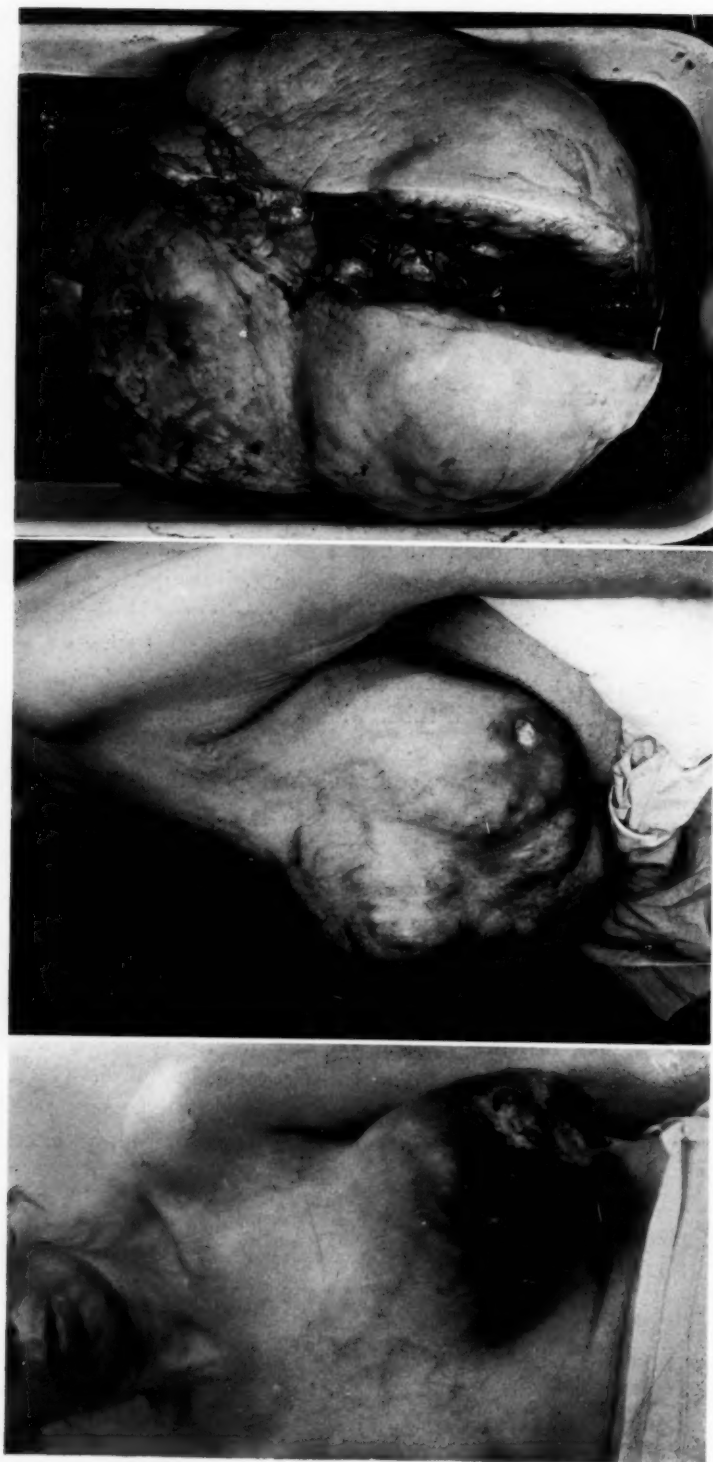
FIG. 1.—Photograph of Case III on admission.   FIG. 2.—Photograph of Case VII on admission.   FIG. 3.—Photograph of specimen, Case VII, after removal of the breast.

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skin with ulceration. Œdema, hæmorrhage, necrosis, and suppuration complicate the advanced stages. In some cases myxomatous changes and overgrowth of blood-vessels are prominent."

Ewing also states, "Labbe and Coyne early pointed out that nearly half the cases represent a malignant transformation of a long-standing fibro-adenoma, and that gestation, lactation, and trauma appear to be exciting causes of the change." In our seven cases there was no history of injury, lactation or recent gestation. One of our cases (Case VI) gave a history of a tumor of forty years' duration.

It is not the purpose of this paper to enter into the discussion of the histopathology, which may or may not be controversial, but to record these seven cases. It was thought that a brief résumé of these histories, pathological findings, together with the treatment and end-results, would be of interest.

One of these cases occurred in a male, seventy-seven years of age; the other six were in females, thirty-two, fifty-seven, fifty-eight, sixty-five, sixty-
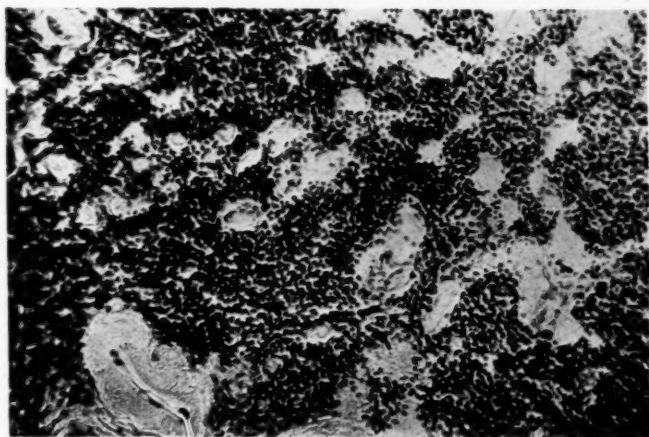
FIG. 4.—Photomicrograph, Case I, lymphosarcoma, showing invasion of muscle.

nine, and seventy-eight years of age. Gross observed a case as young as nine years, another as old as seventy-five years; the average age is reported as between thirty and fifty years.

CASE I.—A woman, aged sixty-nine years, married, consulted us because of a tumor in the right breast which was hard but movable on the underlying tissue, not involving the skin. No history of injury. Small palpable nodes were felt in the axilla. Radical removal done November 8, 1918. During the period 1918 to 1923 she developed widespread metastases, one of which occurred behind the left eye. These were controlled for a period of nearly five years by irradiation. Her blood Wassermann was two plus on admission and she was given specific treatment. She was lost trace of after August, 1923, (four years, nine months from the time of admission).

The histological picture (Fig. 4) shows a typical lymphosarcoma. The cells making up the tumor are of lymphocytic type. The orderly arrangement of the lymphoid tissue is entirely lost with the absence of germinal centres, and so forth. Karyokineisis is in places very profuse, and while, in general, it is normal in type, frequent irregular figures are found in some fields. Infiltration of the tumor-cells in large masses and in small

groups is noted throughout the breast tissue and into the underlying muscle. Some of the smaller blood-vessels show an endarteritis while others are filled with tumor-cells. Some increase in fibrous tissue is noted, particularly just ahead of the advancing edges of the tumor.

CASE II.—A woman, aged sixty-five years, admitted November 29, 1920. Married twenty-seven years, one stillbirth, no other pregnancies. In May, 1920, she noticed a small growth, the size of a kernel of corn, in the left breast; no history of injury. It grew larger and the breast was removed in September, 1920. The histological diagnosis of tissue removed was spindle-cell sarcoma. The blood Wassermann was negative. On examination there was a scar from the apex of the axilla to the free border of the ribs. She was given prophylactic X-ray treatments following the radical amputation and remained free from the disease until her death from cerebral hæmorrhage, December 17, 1929, nine years after admission.
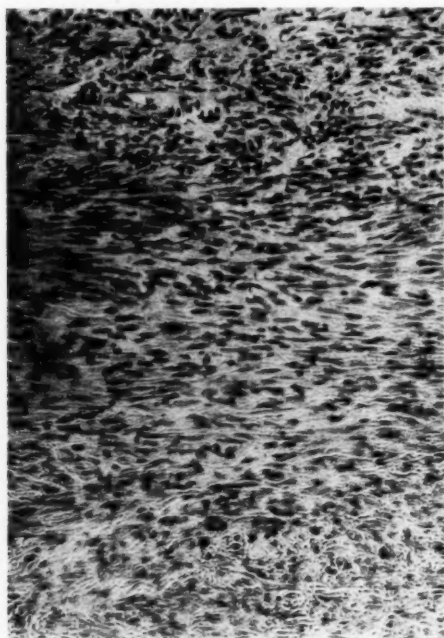
FIG. 5.—Photomicrograph, Case III, showing spindle-cell areas.
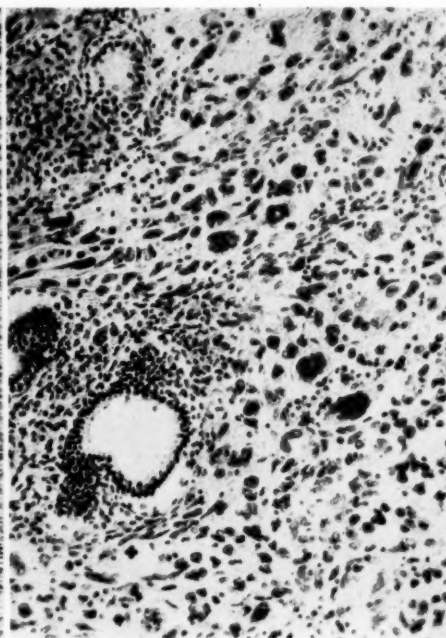
FIG. 6.—Photomicrograph, Case III, spindle-cell sarcoma, showing invasion of breast tissue.

Histological examination shows a tumor made up of spindle cells. The growth does not appear to be particularly malignant. Karyokineisis, while fairly frequent in some areas, is largely confined to the centre of the tumor mass. Very few irregular mitotic figures appear. The tumor is fairly well encapsulated with a fibrous-tissue covering and apparently does not invade the underlying muscle.

CASE III.—A woman, aged thirty-two years, admitted March 23, 1923. Married eleven years, three children alive and well, third pregnancy was a miscarriage at three months. Four months previous to admission she had noticed a small lump in the breast which she poulticed and to which she applied various ointments. No history of injury. Blood Wassermann was negative. At the time of examination there was a large fungating mass involving the whole left breast, with metastases in the axilla. The skin was ulcerated, red and breaking down. (Fig. 1.) She was subjected to high-voltage X-ray and one week later a dinner plate excision of the broken-down tumor was

done. The histological diagnosis was sarcoma. She died in two months from mediastinal involvement.

Histological study shows a very active tumor of the spindle-cell type. There is an unusual number of dividing cells, many of which show irregular mitotic figures. In some fields round and giant cells predominate. The giant cells are unusually large and are both mononuclear and polynuclear types. Lymphocytic infiltration is particularly prominent in these areas. Other portions of the tumor show a typical spindle-cell sarcoma, with the usual spindle-shape cells of fairly uniform size. Infiltration of the glandular tissue of the breast is marked throughout and the tumor nowhere shows encapsulation. Blood channels lined by tumor-cells are found in all portions of the tumor. In addition, some fields show acute inflammatory reaction as evidenced by the presence of many neutrophilic and eosinophilic polymorphonuclear leucocytes and plasma-cells. (Figs. 5 and 6.)
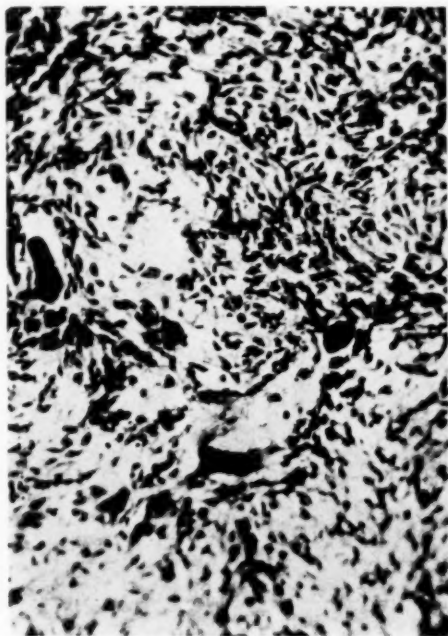
FIG. 7.—Photomicrograph, Case V, showing myxo-fibro-osteosarcoma.   FIG. 8.—Photomicrograph, Case VI, showing mixed-cell type sarcoma.
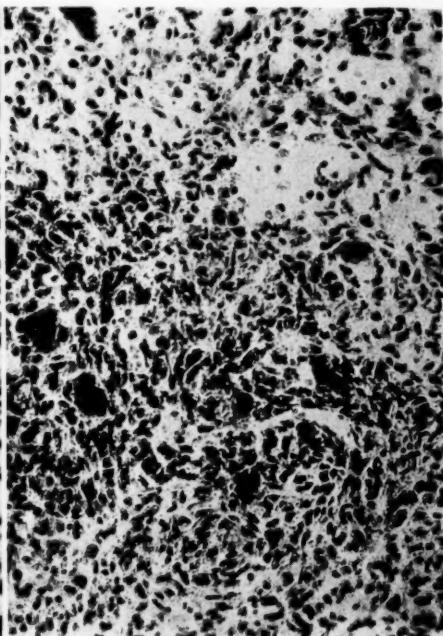
CASE IV.—A male, aged seventy-seven years, admitted August 7, 1925. Married fifty-one years. Gave a history of noticing soreness and a drawing sensation in the left breast one and one-half years ago; after a short time he noticed a lump and had considerable pain. No history of injury. Tumor tissue had been removed from the left breast June 17, 1925, histological report of which was spindle-cell sarcoma. Blood Wassermann was negative. On examination there was a large symmetrical mass in the upper outer quadrant of the left breast which seemed to involve the pectoral muscles; it felt hard. There was a large metastatic node in the axilla. The incision, through which section had been removed, was healed fairly well. He received a course of high-voltage X-ray, but the disease progressed and he died October 26, 1925, two and one-half months after admission.

The histological picture is that of a typical spindle-cell sarcoma. The tumor cells are of uniform size and shape. Mitotic figures are frequent. There is some lympho-

cytic infiltration. No encapsulation is noted and the tumor is definitely infiltrative in character. Blood channels lined with tumor-cells are noted. The pectoral muscle is involved, as are the axillary tissues.

CASE V.—A woman, aged fifty-seven years, unmarried. First seen November 11, 1925, complaining of a tumor mass in the right breast. She gave a history of a small nodule in the breast at the age of sixteen, which had remained stationary for a period of about forty years, and then suddenly (one year before admission) began to grow very rapidly during an attack of acute articular rheumatism. No history of injury. Blood Wassermann was negative. Examination revealed a globular swelling in the outer half of the breast, red from recent plaster application, and it seemed cystic in places. The tumor mass was removed by a local excision and a little later simple mastectomy was performed, after which there was no local recurrence but she died from intrathoracic
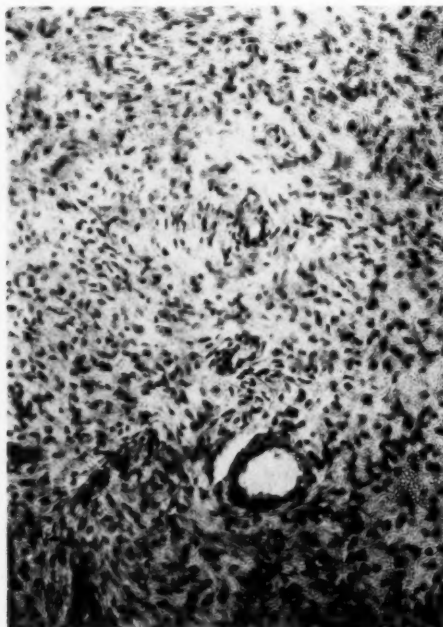
FIG. 9.—Photomicrograph, Case VII, showing spindle-cell areas.

FIG. 10.—Photomicrograph, Case VII, an area showing myxomatous tissue.

metastasis October 19, 1926. The histological diagnosis was myxofibro-osteosarcoma. She received post-operative high-voltage X-ray treatment.

The histological picture furnished by sections of this tumor are decidedly unusual. The tumor is largely made up of cells of embryonic connective-tissue type, many of these being myxomatous in character. In addition, numerous giant cells with small multiple nuclei are liberally scattered throughout the tumor mass. Small areas of typical bone are occasionally found and these are always in close apposition to the above-mentioned giant cells. The tumor is not encapsulated and contains blood channels lined by the tumor-cells. (Fig. 7.)

CASE VI.—A woman, aged fifty-eight years, seen January 20, 1926. Married twenty-six years, no pregnancies. One sister died of cancer of the uterus. She gave a history of first noticing a lump one month previous to admission, in the upper outer quadrant of the right breast. This tumor began to grow and there was some swelling under the arm. No history of injury. Blood Wassermann was negative. Examination revealed a tender

SARCOMA OF THE BREAST

nodule in the upper outer quadrant of the right breast, no palpable nodes. Radical operation was performed on the right breast and the histological diagnosis was sarcoma of the breast, axillary nodes not involved. Subsequently she received high-voltage X-ray treatment. There was no local recurrence but the patient died October 20, 1928, from intrathoracic and abdominal metastases. (Two years, nine months from the time of admission.)

Sections show a sarcoma composes of spindle, round and giant cells, areas of tumor tissue are interspersed with wide bands of dense fibrous connective tissue. In places the tumor shows definite myxomatous change. The giant cells are large and contain, as a rule, many small oval nuclei. The histological picture suggests the sarcomatous degenerations of a fibro-adenoma, as in places remnants of glandular tissue are found both in the tumor areas and in the fibrous-tissue bands. The tumor is definitely infiltrative in character and invasion of both breast tissue and of subjacent muscle are noted. (Fig. 8.)

CASE VII.—A woman, aged seventy-eight years, single, consulted us in October, 1931, because of a tremendously large tumor of the left breast. She gave a history of a tumor which was noticed eight years prior to her admission and which gradually grew to the size shown in the picture and which she was obliged to support on her left arm when walking. (Fig. 2.) It measured sixty-three centimetres from the top of the breast to the under surfaces of the breast, thirty centimetres in diameter and weighed about sixteen pounds. (Fig. 3.) In two places the skin looked as though it might ulcerate. Small, soft lymph-nodes were felt in the axilla. No history of injury. Blood Wassermann was negative. Chest plate was negative. In view of the discomfort operation was decided upon in spite of her advanced age. The tumor mass, together with a portion of the pectoralis major, was removed by a transverse incision, no attempt being made to do anything in a radical way. The wound healed kindly and she was subjected to high-voltage irradiation. At the present writing (February, 1932) her general health is greatly improved and there is no evidence of recurrence. Histological diagnosis was myxofibrosarcoma.

A very large breast was received in the laboratory; it weighed sixteen pounds, seven ounces, was roughly globular in shape and approximately thirty centimetres in diameter. The lower portion of the breast, below the nipple, presented a somewhat nodular appearance with stretching of the skin but no definite ulceration. On gross section of the breast, a dense white fibrous growth, in places attached to the skin surface, was disclosed. This tumor showed a glistening gelatinous surface and in places the substance is translucent. Some hæmorrhagic areas were found scattered throughout the tumor and a few cysts filled with thin, stringy, gelatinous fluid.

Microscopical sections showed a connective-tissue tumor made up of fibrous connective-tissue cells of embryonic type with, in many places, large areas where myxomatous changes had occurred. Some areas of necrosis are found scattered throughout the section. Marked proliferation of the smaller blood-vessels was a rather general occurrence throughout the tumor with some areas of hæmorrhagic deposit. In some fields the tumor has become more cellular with the presence of many spindle-shaped cells.

Diagnosis.—Myxofibrosarcoma. (Figs. 9 and 10.)

BIBLIOGRAPHY

[1] D'Aunoy, and Wright: ANNALS OF SURGERY, vol. xcii, 1930.
[2] Geist, and Wilensky: ANNALS OF SURGERY, vol. lxii, 1915.
[3] Deaver, and McFarland: The Breast: Anomalies, Diseases, Treatment, 1917.
[4] Ewing: Neoplastic Diseases, 1928.

CANCER IN ARMY VETERANS *

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This study was conducted with the coöperation of the hospitals of the Veterans' Administration, Army, Navy, and U. S. Public Health service.

Included in this study were 319 cases of malignant tumors. Of this number, 317 were males and two were females. Three hundred thirteen were white patients and six were colored. Two hundred eighty-eight, or 90.3 per cent., of the 319 patients were born in the United States; and thirty-one were born in foreign countries. Two hundred fifty-nine, or 81.2 per cent. of the malignant tumors were carcinoma; forty-nine, or 15.4 per cent., were sarcoma; and eleven tumors were hypernephroma, endothelioma, glioma, teratoma, or unclassified neoplasms.

Of the patients under treatment for cancer which have been the subject of this study, 68.7 per cent. were veterans of the World War, 26.6 per cent. were veterans of the Spanish-American War, and 4.7 per cent. were veterans of "Other Wars or Expeditions."

Since about 95 per cent. of hospitalized patients are veterans of the World War, little importance may be placed upon the above figures, except the per cent. of veterans of the Spanish-American War hospitalized for cancer is high considering the average age of these veterans and the fact that there were approximately 234,931 alive in 1930 as compared with 4,330,598 World War veterans.

Social Status.—Of 319 ex-service patients with malignant tumors, 78.4 per cent. were or had been married, and 21.6 per cent. were single.

A previous study of 1,000 hospitalized Veterans' Administration patients under treatment for various conditions showed that 62.5 per cent. were married and 30.5 per cent. were single. It is thus seen that the per cent. of ex-service men with malignant tumors who are, or had been married, exceeds the per cent. of the control group of hospitalized patients.

Sixty-seven and one-tenth per cent. were from urban communities, while 31 per cent. were from rural sections; in 1.9 per cent. of the group the place of residence was not indicated.

The probable reasons for the preponderance of cancer in urban communities are: (1) The majority of the ex-service men are residents of urban communities; (2) more frequent and better opportunities for medical examinations are possible in cities and there is therefore greater likelihood of the diagnosis of cancer.

Hereditary or Familial History.—There were fifty-two cases of malignant tumors with a positive hereditary or familial history or both. Thirty-six cases, or 69.2 per cent., gave a hereditary history of cancer; eleven, or 21.2 per cent., gave a familial history; and five, or 9.6 per cent., gave both a familial and hereditary history of cancer.

Of the fifty-two cases, forty-four were affected with carcinoma; seven were affected with sarcoma; and one was a case of endothelioma.

In those cases in which there was a hereditary history of cancer, the mother was the member of the family most frequently affected. In the group in which there was a familial history of malignancy the sister was the member of the family most frequently affected. In those cases in which there was a combined familial and hereditary history of cancer the father and brother were the members of the family most frequently affected.

While the study of this group shows that but 16.3 per cent. of the total number gave a hereditary or familial history of cancer and does not definitely indicate the part played by heredity in the causation of the disease, nevertheless, consideration must be given the fact that the majority of the ex-service men have not as yet reached the cancer-age periods when malignant tumors develop as the result of such factors as trauma and irritation, biological changes of the tissue cells, chronic inflammatory changes and malignant transformation of benign neoplasms. As the ex-service men grow older and the opportunities for the development of cancer become greater it is to be expected that the hereditary and familial influences will assert themselves and contribute their share in the causation of the disease so that the number of cases with a hereditary or familial history will be markedly increased.

Site of Tumors.—The most frequent were the skin, 19.4 per cent.; the lip, 14.7 per cent.; the stomach, 11 per cent.; the lymph-nodes, 7.2 per cent.; the rectum, 6.3 per cent.; the buccal cavity, 4.4 per cent.; the urinary bladder, 4.1 per cent.

The Age Distribution of Carcinoma.—In a series of 259 patients, it was found that the largest number were within the age groups thirty-five to forty, thirty to thirty-five, forty to forty-five, and fifty to fifty-five years. In a series of forty-nine cases of sarcoma, the largest number of patients were within age groups thirty to thirty-five, thirty-five to forty, and twenty-five to thirty years. A study of the age distribution of the other types of tumors, comprising eleven cases, showed that the largest number, six, were within the age group thirty-five to forty.

From the above it would appear that the age group thirty-five to forty is the most critical period from the standpoint of the onset and incidence of malignant disease. In susceptible individuals all factors which tend to result in malignant tumors, such as continual irritation, chronic inflammation, benign growths, *etc.*, should receive appropriate treatment prior to or during this period with a view to the prevention of cancer.

Ewing maintains that senile atrophy of tissues and organs, replacement fibrosis, and arteriosclerosis create local conditions which favor the develop-

ment of some cancers. He states that the main factor which accounts for the high incidence of cancer in the aged is the lapse of time which permits the natural termination in cancer of processes which have their inception in adult life, in youth, in infancy, or even *in utero*. That the majority of tumors of old age may be thus explained cannot be asserted without much more evidence than is now available, but appears highly probable.

Age at Time of Onset of Cancer.—In 1851, Lebert made a study of the ages at the time of the onset of various types of malignant tumors in a series of cases and found that the mean age for the whole group was fifty-one years. In 1930, Pack and LeFevre found that the mean age of the onset of malignant tumors in a group of cases was 53.9 years.

Of the group of 319 ex-service patients, the histories of 303 indicated that the mean age at the time of the onset of cancer varied from twenty-nine years in the case of teratoma of the genito-urinary tract to a mean age of fifty-two years in the case of sarcoma of the digestive tract. The mean age of the whole group at the time of onset of cancer was forty-three years. It is further noted that there is a difference of ten years between Pack's and LeFevre's findings and the findings in this study. The explanation is that we are dealing with a select group of ex-service men of an average age of approximately forty years.

Weight at Time of Inception of Cancer.—Inasmuch as little information is available upon this subject it was decided to include in this investigation a study of the weight of the patients at the time of the onset of cancer. The weight in each case was correlated with the age and the height of the patient and a determination was made whether or not it was within normal range $(+ 5$ per cent. to $- 5$ per cent.). If above or below the normal range an estimate was made of the per cent. of increase or decrease of weight as compared with normal. In 226 patients with malignant tumors, 39.8 per cent. of the number were below the standard weight at the time of onset of cancer; 26.1 per cent. were above the standard weight; and 34.1 per cent. were within the normal standard range of weight. Of the fifty-nine cases above the standard weight at the time of the onset of cancer, the largest group, twenty-one cases, showed a deviation of 6 to 10 per cent.; and the next largest group, nineteen cases, showed an increase over normal weight of 11 to 20 per cent. Of the ninety cases below standard weight at the time of the onset of cancer, the largest group, consisting of forty-nine cases, showed a decrease from normal weight of 11 to 20 per cent.; and the next largest group, of thirty cases, showed a decrease from the normal weight of 6 to 10 per cent.

From the above information it would appear that there is no correlation of weight with the inception of cancer. While an appreciable number of patients of the group were overweight in the early stages of the disease, the majority were either underweight or within the normal range of weight for height and age.

Occupation.—That certain occupations predispose to the inception of cancer is an established fact. Some of the occupations which are etiological fac-

tors of cancer are: Chimney sweeping, gardening, work in coal-tar and pitch industries, and X-ray work. W. Roger Williams maintains that farm laborers, gardeners, sailors and those who follow out-door occupations are unduly prone to cancer of the lower lip.

In a study of the occupation of 238 members of the group, it was found that 125, or 52.9 per cent., were engaged in technical or industrial pursuits; fifty-eight, or 24.3 per cent., were engaged in agriculture or allied pursuits; forty-five, or 18.8 per cent., were engaged in commercial pursuits; and ten, or 4 per cent., were in various professions.

In order to ascertain whether or not there was a relationship of occupation to the causation of cancer, a study was made of 128 members of the group with malignant tumors of various organs and sites, forty-eight of which were cases of malignant neoplasms of the skin or mucous membrane. Of forty-eight cases of cancer of the skin or mucous membrane, in twenty-five instances it was present in farmers and ranchers. It is realized, of course, that the actinic rays and the outdoor life of the farmer or rancher may act as irritants and be factors in the causation of cancer of the skin. There was no other indication of a relationship existing between any occupation and cancer of a particular organ or site.

Chronic Irritation or Chronic Inflammation as Forerunner of Malignant Neoplasms.—Of 319 cases of cancer, 128, or 40 per cent. of the group, gave a well-defined history of a previous irritation or chronic inflammatory process. This is in accord with the views now held by many observers that the development of malignancy is dependent upon: (1) An extrinsic factor of irritation or inflammation; (2) an inherited constitutional cancer susceptibility; (3) an inherited organ or tissue predisposition. The opinion also prevails that the irritation or inflammation may in some instances take the place of the local organ or tissue predisposition.

The relationship of trauma or inflammation to the development of cancer is not thoroughly understood but the following hypothesis has been formulated to explain the mechanism of the transition of normal tissue cells to malignant cells:

Trauma of living cells or a chronic inflammatory process is usually followed by an attempt at repair, and leads to a temporary change of "potential" growth ability to "kinetic" growth ability, *i.e.*, it leads to a temporary elimination of "growth restraint," a property possessed by matured tissues or organs. What follows, then, is a multiplication of the cells in the traumatized or inflamed area at an unnatural and accelerated rate, due to the absence of the property of "growth restraint" and the loss by the cells of the normal property of physiological repair.

One hundred, or 78.1 per cent., of the total of 128 patients with a history of chronic irritation or inflammation, had carcinomas; twenty-six, or 20.3 per cent., had sarcomas; one was a case of endothelioma; and one was a case of teratoma. The most frequent sites of malignant tumors in which there was a previous history of chronic irritation or chronic inflammation

were: The skin or mucous membrane, the digestive tract, the genito-urinary system, the buccal cavity, the bones and the lymphatic system.

Use of Tobacco.—Of the total number of 319 cases, it was found that in seventy-six instances the malignant tumors might be attributable to smoking. The principal sites of the cancers were as follows: Forty-five cases were on the lip; nine were in the mouth; seven were on the tongue; and five were cases of carcinoma of the larynx. The largest number, twenty-six, or 34.2 per cent., were cigarette smokers; thirteen, or 17.1 per cent., were pipe smokers; and eight, or 10.5 per cent., were cigar smokers.

Twelve, or 15.8 per cent., of the group did not use tobacco; seven of these twelve patients had carcinoma of the lip.

Pre-Cancerous State.—In reviewing the clinical records of the group of 319 cases, it was found that eighty-eight, or 27.6 per cent., gave a history of having had some forerunner or pre-cancerous condition prior to the actual development of cancer. The pre-cancerous condition was of a varied type, such as a chronic ulceration or fissure formation of the skin, pigmented mole, keratosis, gastric ulceration, papilloma, adenoma, *etc.*

While but 27.6 per cent. of the patients gave clinical evidence of the presence of a pre-cancerous condition, the probabilities are that the number would have been greater if special means had been used to detect this condition; it is frequently symptomless and is difficult of diagnosis, particularly if it is situated in deep-seated organs or tissues.

Malignant disease is not a spontaneous, fully developed condition, but is the result of evolutionary changes of tissue cells through various stages, which, at first, are benign and subsequently assume malignant qualities. The changes through which tissue cells pass may be inflammatory, hyperplastic or neoplastic—any of these may terminate in cancer.

Characteristics of Malignant Neoplasms.—The characteristics of malignant neoplasms are dependent upon the location of the growth and upon the type of tumor. If the tumor is preponderantly cellular it is usually of a soft consistency. On the other hand, if much fibrous connective tissue is present in the growth, induration is the rule.

In reviewing the histories of 297 patients with malignant tumors, it was found that the most common characteristics were a combination of induration and ulceration; the next most frequent characteristic was induration; ulceration was next in frequency; and a combined tumor formation and induration appeared to be the next most common characteristic.

Early Symptoms of Malignant Tumors.—In view of the fact the favorable outcome of cancer is dependent upon the institution of early treatment, it is highly desirable that one know the initial symptoms and signs of the disease so that an early diagnosis may be made. At times, this is a difficult matter, inasmuch as tumors in certain locations are symptomless or possess no definite or characteristic signs by means of which a diagnosis may be made.

Of 259 Veterans' Administration patients affected with carcinoma, the most frequent symptoms and signs which first directed attention to the malignant neoplasm were ulceration, tumor formation, pain, bleeding, and loss of weight.

The symptoms and signs most frequently found in the early stages of forty-nine cases of sarcoma were: tumor formation, pain, loss of weight, and ulceration. The group of tumors other than carcinoma and sarcoma, eleven in number, manifested the following symptoms and signs during the early stages of the disease: tumor formation and pain.

In the consideration of the total number of 319 cases, the most frequent early symptoms and signs of malignant disease noted were: tumor formation, pain, ulceration, bleeding, and loss of weight.

Symptoms of Cancer During Hospitalization.—While cancer is at first localized and the symptoms and signs present are referable to the site of the tumor, there is a gradual development of constitutional symptoms as the disease progresses. The principal symptoms and signs noted among the 319 patients under hospitalization at the time of this study, in the order of frequency, were: pain, tumor, loss of weight, ulceration, loss of appetite, cachexia, anæmia, bleeding, discharge, insomnia, and nervousness.

Rate of Growth.—A study of the rate of growth of neoplasms in the group of ex-service patients under hospitalization for malignant disease shows that in 62.7 per cent. the rate of growth of the tumor was slow; in 36.1 per cent. of the cases there was a rapid growth; and in 1.2 per cent. of the cases the rate of growth was unknown. It was further noted that the per cent. of sarcomas giving a history of rapid growth was greater than the per cent. of carcinomas.

Incidence of Pain at Time of Onset of Malignant Tumor.—In a review of the clinical data it was found that 304 of the group gave a history of the presence or absence of pain at the time of the origin of malignant disease, while in fifteen instances this information was not recorded.

Of the 304 cases, 140, or 46.0 per cent., gave a definite history of pain at the time of the onset of the growth; eighty-nine, or 29.3 per cent., developed pain after the onset of the growth; while seventy-five, or 24.7 per cent., had no pain during the course of the neoplastic disease. Of seventy-two cases of carcinoma of the digestive tract, fifty-three, or 73.6 per cent., gave a positive history of pain at the time of the onset of the growth. Of 104 cases of carcinoma of the skin or mucous membrane, twenty-eight, or 26.9 per cent., gave a positive history of pain at the time of the onset of the malignant growth; forty-eight, or 46.2 per cent., gave a negative history of pain; while twenty-eight, or 26.9 per cent., developed pain after the onset of the tumor. It was further noted that in seventeen cases of sarcoma of the lymphatic system, six, or 35.3 per cent., gave a positive history of pain at the time of the onset of the malignant tumor; six, or 35.3 per cent., gave a negative history of pain; and five, or 29.4 per cent., developed pain after the onset of the malignant tumor.

Length of Time Between Onset of Cancer and Appearance of Pain.—
It was stated that eighty-nine, or 29.3 per cent., of a total of 304 patients with
malignant tumors developed pain after the onset of the neoplasm. Further
study was made of the clinical records of this group to ascertain the known
length of time extending from the date of onset of cancer to the date of the
appearance of pain. This information was obtainable in seventy-five cases
and it was found that the length of time varied, depending upon the type of
malignant tumor as well as upon the organ or site of the disease.

For instance, in twelve cases of carcinoma of the digestive tract the
shortest length of time from the onset of the tumor to the appearance of
pain was two weeks; the longest period was 144 months; and the average
period was 22.4 months. For sixty cases of carcinoma of various kinds the
shortest length of time before pain appeared was two weeks; the longest
period was 144 months; and the average period was 20.4 months. For
thirteen cases of sarcoma of all kinds the shortest length of time before pain
appeared was one month; and the longest period was seventy-two months;
the average period was sixteen months.

Taking the whole group of seventy-five cases of cancer into consideration,
the shortest period from the time of the onset of the disease to the appearance
of pain was two weeks; the longest period was 144 months; and the average
period was 20.7 months.

The above data would indicate that frequently pain does not appear in the
early stages of cancer. The patient may therefore not be cognizant of the
nature of the condition, inasmuch as the other symptoms present are not
suggestive of a neoplasm nor are they serious enough for the patient to seek
medical advice.

Delayed Diagnosis of Cancer.—It is a well-known fact that the principal
cause of the hopelessness of the treatment of cancer is that it is instituted
too late; the reason being that there is a delay in making a definite diagnosis.
Frequently, when the patient is first seen by the physician, the condition
is in a pre-cancerous state, *i.e.*, it is either a chronic inflammatory proc-
ess or perhaps a benign neoplasm, which may be responsible for the in-
sidious and vague symptoms that are not considered alarming by the patient.
Frequently there is no pain or discomfort associated with these pre-cancerous
conditions.

If medical or surgical advice is sought the physician may overlook the
potential seriousness of the condition and administer symptomatic treatment
only. Later, when the condition has become manifestly malignant and sub-
jective and objective symptoms arise, which again force the patient to the
physician, the seriousness of the disease is noted and radical remedial
measures are instituted. Unfortunately, by this time the cancer has reached
such an advanced stage that little benefit can be derived from the treatment
administered.

In order to study this phase of cancer the clinical data of a group of
patients were reviewed and it was found that of 315 cases, 201 were treated

for various conditions before a diagnosis of malignant tumor was made; in sixty-two instances there was no treatment prior to the diagnosis of malignant tumor; in fifty-two instances there was no record of any previous treatment nor could any information on this point be obtained.

It is of interest that of the 201 cases who were treated for some non-neoplastic disease before a definite diagnosis of cancer was made, 105, or 52.2 per cent., were treated for periods less than one year; twenty-five, or 12.4 per cent., from one to two years; altogether 85 per cent. of the group were treated for various periods up to six years. In some instances, patients were treated as long as twenty years before a diagnosis of cancer was definitely made.

Metastases.—An attempt was made to ascertain the number of cases showing metastatic growths in the group of 319 patients under hospitalization for cancer. The largest number of these patients were in the younger age groups. One hundred and twelve, or 35.1 per cent., showed the presence of metastases, and 207, or 64.9 per cent., gave no evidence of metastatic involvement.

The most common tumors and their sites showing metastases, in the order of frequency, were: carcinoma of the digestive tract, carcinoma of the skin or mucous membrane, sarcoma of the lymphatic system, carcinoma of the buccal cavity, and carcinoma of the genito-urinary tract.

Coëxisting Diseases.—The relationship of certain diseases to cancer has been frequently discussed but no definite conclusion has been reached except that it has been held that active tuberculosis seldom coëxists with malignant tumors. Attempts have been made by many observers to show a relationship of syphilis, rheumatism and diabetes mellitus to cancer, but the findings have not been convincing.

Syphilis.—The consensus of opinion appears to be that the relationship of syphilis to cancer is very remote. Among the 319 patients with cancer, syphilis was a coëxisting disease in 2.1 per cent. of the cases.

Arthritis or Rheumatism.—A good deal of information is found in the literature on the relationship of arthritis and rheumatism to cancer, but the conclusions reached are not based upon reliable evidence. Of the total number of 319 cases of cancer, 6.9 per cent. had coëxisting arthritides or rheumatic affections.

Diabetes Mellitus.—Some observers are of the opinion that there is a well-defined correlation of diabetes mellitus with cancer. The over-indulgence of food so commonly encountered in diabetes mellitus may result in abnormal metabolic changes which later may become a predisposing factor of cancer. Of the group of 319 patients, 1.9 per cent. had a coëxisting diabetic condition.

Tuberculosis.—Rokitansky, Pearl, and others have shown that there is an antagonism between tuberculosis and cancer. On the other hand, Carlson and Bell are of the opinion that the findings of Pearl were arrived at by a statistical method to which they objected. Fortune holds that the subject with

tuberculosis is less apt to acquire cancer only because he succumbs to tuberculosis before he reaches the cancer age.

In a study of the necropsy material of the Veterans' Administration, the writer found that cancer was more prevalent among non-tuberculous beneficiaries than in those with tuberculosis, and, furthermore, that tuberculosis was more frequent among non-cancerous cases than in those with malignant neoplasms. However, there is nothing in the data to show that there is a biological antagonism of one disease against the other.

Of the 319 cases of cancer, four had a coëxisting active pulmonary tuberculosis; one had inactive pulmonary tuberculosis; five were cases of arrested pulmonary tuberculosis; and one was a case of tuberculosis of the dorsal vertebræ.

Known Duration of Malignant Neoplasms.—In a study of the duration of malignant neoplasms in New York State it was found that among 814 males, 39.4 per cent. had a known duration of less than one year; 57.2 per cent. had a known duration of from one to four years; and in 3.4 per cent. of the cases the duration was five years or over. The large majority of cancer deaths followed a previous known duration of from six to twenty-four months.

The known duration of cancer as estimated in this study extends from the date of onset of the disease to the date of death. It is noted that in the case of sixty-six carcinomas 37.9 per cent. showed a known duration of less than one year; 24.3 per cent. from two to three years; and 19.7 per cent. from one to two years. Of twenty sarcomas 40 per cent. showed a known duration of less than one year and 40 per cent. from one to two years. Taking the whole group of eighty-nine cases into consideration, 38.2 per cent. had a known duration of less than one year; 25.8 per cent. from one to two years; and 18 per cent. from two to three years. Among sixty-six cases of carcinoma, the minimum known duration was two months; the maximum duration was 156 months; and the mean known duration was 28.3 months. Of twenty cases of sarcoma, the minimum known duration was two months; the maximum duration was sixty months; and the mean known duration was 18.2 months. Taking the group of eighty-nine cases into consideration, the minimum known duration of all forms of malignancy was two months; the maximum duration was 156 months; and the mean known duration was 25.6 months.

Living Cases.—The known duration of malignant neoplasms among a group of 203 living veterans whose clinical records contained this particular information extends from the date of onset of the condition to the date of this study (September, 1930). It was noted that in the case of 172 carcinomas, 23.3 per cent. had a known duration of less than one year; 23.3 per cent. from one to two years; and 16.3 per cent. from two to three years. Of twenty-six sarcomas 15.4 per cent. showed a known duration of from ten to eleven years; 15.4 per cent. from five to six years; 11.6 per cent. from twelve to thirteen years; 11.6 per cent. for periods less than one year; 11.6

per cent. from one to two years; and 11.6 per cent. from two to three years. Taking the whole group of living veterans with cancer into consideration, 203 in number, 22.7 per cent., showed a known duration of less than one year; 21.2 per cent. from one to two years; and 15.8 per cent. from two to three years. Among 172 carcinomas the minimum known duration was one month; the maximum known duration was 216 months; and the mean known duration was 42.3 months. Of twenty-six sarcomas the minimum known duration was six months; the maximum known duration was 156 months; and the mean known duration was 68.8 months. Considering the whole group of 203 living cases the minimum known duration was one month; the maximum known duration was 216 months; and the mean known duration was 45.5 months.

It is noted that the mean known duration of the living sarcoma cases was greater than the mean known duration of the cases of carcinoma; while among the deceased cases of malignant neoplasms the mean known duration of cases of sarcoma was less than the mean known duration of cases of carcinoma. The mean known duration of all of the deceased cases of cancer was 25.6 months while in the living cases it is 45.5 months up to the date of this study.

Classification of Patients with Cancer According to Activity.—The outstanding symptoms of cancer are weakness and loss of strength with the result that the patient is unable to carry on his accustomed work. There is therefore an impairment of his economic efficiency and a reduced earning capacity. The classification of the activity of the patients with cancer used in this study is similar to that used by the American Heart Association in the grouping of patients affected with heart disease. Altogether, 318 of the patients were classified.

It is noted that 25.8 per cent. were able to carry on ordinary physical activity; in 13.8 per cent. of the group the activity was slightly limited; in 22.3 per cent. activity was greatly limited; and 38.1 per cent. of the patients were unable to carry on any physical activity, *i.e.*, they were bed patients.

Of the patients who were able to carry on ordinary physical activity, the largest number were among those affected with carcinoma of the skin or mucous membrane. Of the patients whose activity was slightly limited, the largest number were among cases of carcinoma of the skin or mucous membrane. Of the patients whose activity was greatly limited the largest number were among those with carcinoma of the digestive tract. Of the patients who were unable to carry on any physical activity and were confined to bed, the largest number were among those with carcinoma of the digestive tract.

The activity of patients with cancer is dependent to a considerable extent upon the site as well as upon the stage of the disease. Frequently tumors give rise to constitutional symptomatology during the incipient stages so that activity is greatly limited from the first. This is commonly found in tumors of the digestive tract and of the lymphatic system. As a general

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rule, however, constitutional symptoms of cancer develop in the later stages, and when this occurs the activity of the patient is usually very much curtailed.

Treatment.—In the treatment of the group of patients under hospitalization for malignant neoplasms the following regimens were used: (1) Symptomatic therapy, (2) X-ray, (3) radium, (4) surgery, (5) cautery, (6) Coley's toxin. In addition, a number of combinations of these regimens were utilized—the kind of treatment depending upon the site and type of malignant tumor as well as upon the stage of the disease.

In the hospitalization of a group of 315 patients with malignant tumors the most frequent forms of treatment used were: (1) Surgery and X-ray, (2) surgery, (3) symptomatic therapy, (4) X-ray, (5) surgery, X-ray and radium, (6) radium, (7) surgery and radium.

Result of Treatment.—The result of treatment of malignant tumors depends upon a number of factors, such as: The type of treatment, the type of cancer and the organ affected, the stage of the disease at the time treatment is first instituted, and in addition the outcome of the case is dependent upon whether or not there is glandular involvement and also if metastases are present at the time treatment is administered. It is a well-known fact that malignant neoplasms of certain organs or sites are best treated by certain particular regimens and the results with these regimens are better than if other forms of treatment are used.

Of 315 beneficiaries undergoing hospitalization for cancer, 42.8 per cent. were considered improved upon the termination of the hospitalization; 20 per cent. were unimproved; 5.1 per cent. were worse; and 32.1 per cent. died during the period of hospitalization. The condition of some of the patients was recorded as "cured," but it was thought best to consider them as "improved," inasmuch as sufficient time had not elapsed to justify the former classification.

In explanation of the percentage of deaths (32.1) it may be stated that a large number of the patients were admitted to the hospitals in an advanced stage of the disease, too late to receive benefit from the treatment administered.

A study of the records to ascertain the results with various forms of treatment revealed the following information: Of the twenty-two patients receiving radium treatment, 86.4 per cent. were alive and 13.6 per cent. had died.

Of twenty-eight patients receiving X-ray, radium and surgical treatment, 85.7 per cent. were alive and 14.3 per cent. died. Of fifteen patients receiving radium and surgical treatment, 73.3 per cent. were alive and 26.7 per cent. died. Forty patients received X-ray treatment, and of this number 70 per cent. were alive and 30 per cent. died. Fifty-five patients were treated by means of X-ray and surgery, of which number 69.1 per cent. were alive and 30.9 per cent. died. Twelve patients were treated with X-ray and radium, and of this number 66.6 per cent. were alive and 33.4 per cent. died. Eleven patients were treated by X-ray, surgery and cautery, and of this

number 63.6 per cent. were alive and 36.4 per cent. died. Forty-seven patients were treated by surgical means, of which number 61.7 per cent. were alive and 38.3 per cent. died. Forty-six patients were treated symptomatically, and of this number 41.3 per cent. were alive and 58.7 per cent. died.

A study was made to ascertain the best methods used in the treatment of malignancy of various organs and tissues as judged by the most favorable results, and the following information was obtained:

Carcinoma of the Skin or Mucous Membrane.—There were 104 patients treated. The best results were obtained by the use of the following procedures in the order named: (*a*) surgery, (*b*) surgery and cautery, (*c*) radium, and (*d*) X-ray and surgery.

Carcinoma of the Buccal Cavity.—Twenty-three patients were treated for malignancy of the buccal cavity. The best results were obtained by the use of the following procedures in the order named: (*a*) radium, (*b*) cautery, (*c*) radium and X-ray, and (*d*) X-ray, radium and surgery.

Carcinoma of the Digestive Tract.—Seventy-seven patients were under treatment for carcinoma of various portions of the digestive tract. The best results were obtained by the use of: (*a*) surgery and X-ray, and (*b*) X-ray, in the order named.

Carcinoma of the Genito-urinary Tract.—Twenty-one patients were treated for cancer of the genito-urinary tract. The best results were obtained by the use of surgery and X-ray.

Sarcoma of Bone.—Eight patients were treated for this type of malignant neoplasm. The best results were obtained by a combination of X-ray, radium and surgery.

Sarcoma of the Lymphatic System.—Seventeen patients were treated for this form of malignant neoplasm. The best results were obtained by the use of (*a*) X-ray and radium, and (*b*) X-ray, surgery and cautery, in the order named.

CORRELATION OF TYPE OF TREATMENT WITH KNOWN DURATION OF
MALIGNANT NEOPLASMS

The type of treatment as well as the known duration of life following the same were studied for the purpose of ascertaining whether or not there was a correlation between these two factors. The study yielded the following data:

Symptomatic Treatment.—Of a group of nineteen living patients treated symptomatically for malignant neoplasms the average known duration of the disease from the date of onset to the date of this study (September, 1930) was 44.8 months.

Of a group of twenty-seven patients with malignant neoplasms who died and who had been treated symptomatically the average known duration of life following such treatment was 20.7 months.

Radium Therapy.—Of a group of nineteen living patients who had re-

months, was noted in the case of malignant tumors of bone; the shortest known duration, that of nine months, was noted in the case of carcinoma of the tongue.

The average period of time between the onset of the disease and the date of the surgical treatment was 41.5 months. The shortest average time, that of 18.4 months, was in the case of carcinoma of the stomach; the longest average interval, that of seventy-seven months, was in the case of carcinoma of bone.

Thirty-four patients with malignant tumors who died and who had been treated by means of surgery and irradiation had an average known duration of life of 31.1 months. The longest average known duration, that of 54.7 months, was among patients with carcinoma of the skin.

The average period between the onset of the disease and the date of surgical intervention was 9.8 months. The shortest average period of time, that of two months, was recorded in the case of carcinoma of the buccal cavity; the longest average period, that of 23.4 months, was noted in the case of malignancy of the lymph-nodes.

In comparing the average known period of time between the onset of cancer and the date of surgical intervention in those patients who received surgical treatment alone with those who received irradiation and surgical treatment, it is found that on the whole the interval of the patients who underwent surgical treatment was shorter than that of the patients who received both irradiation as well as surgical treatment.

It may be assumed that in the majority of instances irradiation was used first and was later followed by surgery. The known duration of life following the combined surgical and irradiation regimens was longer than that following surgery alone.

Relative Potency of Therapeutic Regimens.—The results with each type of treatment as judged by the largest per cent. of the patients alive upon the termination of the hospital episode were compared, and the following treatment regimens in the order named, were found to be the most effective: (1) radium, (2) surgery and irradiation, (3) X-ray, (4) surgery, (5) X-ray and radium, (6) symptomatic treatment.

Known Duration of Cancer Correlated with Type of Treatment.—Of a group of 213 patients under treatment for cancer and alive at the time of this study the average known duration of the disease was 44.1 months. The longest average known duration, that of fifty-two months, was noted in the case of twenty-eight patients treated with X-ray. The shortest average known duration, that of 35.3 months, was noted in forty-six cases of malignancy treated by means of surgery. Nineteen patients who were treated symptomatically showed an average known duration of 44.8 months.

One hundred of the group of patients under treatment for cancer died during the hospital episode. The average known duration of the disease in this group was 25.9 months. The longest average known duration, that of fifty-three months, was noted in four patients treated with X-ray and radium.

The shortest average known duration, that of 12.7 months, was noted in three patients treated with radium. Twenty-seven patients who died during the hospital episode were treated symptomatically and the average known duration of cancer was 20.7 months.

The Deaths.—Of the 319 cases hospitalized for malignant neoplasms, 101 died during the hospital stay. In this connection it must be understood that beneficiaries are admitted to Veterans' Administration and other Government hospitals upon the presentation of evidence of discharge from the military service. A number of the patients who died during hospitalization were in the terminal stages of cancer upon admission, too far advanced with the disease to be aided by any treatment.

The most frequent sites of the malignant neoplasms of patients dying were: the digestive tract, the skin or mucous membrane, the buccal cavity, the lymphatic system and the genito-urinary tract.

The most frequent causes of death were: Carcinoma of the digestive tract, carcinoma of the buccal cavity, carcinoma of the skin or mucous membrane, sarcoma of the lymphatic system, carcinoma of the genito-urinary tract and surgical shock.

In the group of 101 cases under treatment for malignant neoplasms who died while being hospitalized, seventy-nine, or 78.2 per cent., died from the malignant tumor; and 22, or 21.8, died from other causes. The most frequent causes of death other than malignant tumors were: Surgical shock, hæmorrhage, œdema, and intestinal obstruction.

In the discussion of the age at death of the 101 cases of malignant tumor, it must be understood that we are dealing with a select group of males of an average age of forty years. It will be noted that the ages at death of these patients are below the ages at death from cancer in the general population. The age at death from malignant tumor is dependent upon a number of factors, such as the age at the time of onset, the duration, as well as the type and site of the malignant tumor, and the treatment administered.

In this connection it is desired to point out that certain tumors of young subjects are rapidly growing and highly malignant. The clinical history of such cases is that of a rapid course and high mortality. Broders has shown that the active tissues of youth invite the growth of malignant tumors instead of resisting their spread and the host has little chance for longevity, regardless of the type of treatment administered.

Of the patients who died the largest number, twenty-two, or 21.8 per cent., were within the age groups forty to forty-five and thirty-five to forty; the next largest number, fourteen, or 13.8 per cent., were within the age group thirty to thirty-five. Of seventy-six cases of carcinoma the minimum age was thirty-one; the maximum age was eighty-two; and the mean age was 47.6 years. Of twenty-one cases of sarcoma the minimum age was thirty-one; the maximum age was sixty-eight; and the mean age was 42.5 years. Of the whole group of 101 cases the minimum age at death was thirty-one; the maximum age was eighty-two; and the mean age at death was 46.2 years.

GASTRECTOMY

AN EXPERIMENTAL STUDY*

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Study of the effect of total removal of the different organs of the body has been of value in several respects. It has been determined that some organs are vital, that is, necessary for life, and that others are not. In some instances, knowledge concerning the function of an organ has been revealed by a study of the effect of its removal; in other instances, the method whereby the body compensates for the loss of an organ has been revealed by removal of the organ. Technical methods for the removal of organs have been worked out experimentally. Many of the studies on the effect of removal have been of value to clinical medicine. We shall report here the results of removal of one of the important organs, the stomach.

Hartman[13] noted a condition in which most of the characteristics of pernicious anæmia were associated in a case in which W. J. Mayo had removed the stomach a considerable time previously. This observation emphasized in another way the possible causal relationship between achylia gastrica and pernicious anæmia. At Hartman's suggestion, we undertook a study of the effect of the removal of the stomach of dogs. During several years in which this problem has been under investigation, other cases of pernicious anæmia in which the stomach had been removed have been reported;[19] the stomach has been removed from human beings more frequently;[16 26] a relationship between gastric function and pernicious anæmia has been noted,[6] and newer and apparently more fruitful experimental work on exclusion and removal of the stomach has been described.[9 15]

REVIEW OF THE LITERATURE

Czerny and Kaiser[8] were apparently the first to attempt total removal of the stomach of dogs. A series of operations was performed in which an attempt was made to remove the stomach and to anastomose the duodenum to the œsophagus. One animal survived the operation five years, but at necropsy a small gastric pouch was found. Evidently a minute remnant of stomach was left attached to the œsophagus, for at the time of operation the surgeons were confident that extirpation was complete. Monari[17] attempted the operation on a dog. The animal survived the operation, but at necropsy a piece of

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cardia was found. In like manner a fragment of cardia was found to have been left at operation by Carvallo and Pachon.[4] They concluded that complete extirpation of the stomach of a dog through the abdominal route is not possible, and that the abdominal portion of the œsophagus after resection of the stomach is too short to permit anastomosis. They also removed the stomach of cats, and found that the operation was relatively easy because of a peculiar anatomical arrangement of fibrous bands extending from the diaphragm onto the œsophagus, and the fact that in the cat the abdominal portion of the œsophagus is more extensive than in the dog. In the latter respect the operation on the cat was more comparable to conditions that obtain in man. It was found that healing of the suture line was sufficient at the end of the third day to permit the feeding of solid food. As the most significant condition found at necropsy was pulmonary congestion, they assumed the section of the vagi to be of considerable importance. The only cat that survived operation for a long period lived for seven months. The cat ate normally and gained weight steadily for four months, then refused food, and was fed with a stomach tube. Death occurred soon after forced feeding was discontinued. Carvallo and Pachon[5] concluded that the stomach is not indispensable for the maintenance of life, but that it is important in reflexly initiating a peripheral sensation of hunger.

Grohé[12] attempted total removal of the stomach from the dog, but the only animal to survive had a remnant of cardia.

Carrel, Myer, and Levene[3] performed gastrectomy on two dogs in the course of a study of nitrogen metabolism. Fourteen weeks after the operation, at which time the animals were killed, a small portion of pylorus was found in one of the animals.

Unger reported experiments on dogs by Bettmann[1] in which the stomach was removed through the transthoracic route with the aid of Meltzer-Auer insufflation anæsthesia. The duodenum was anastomosed to the œsophageal stump.

Verson[25] described a similar method for removing the stomach of dogs by the transthoracic route, and a year later he reported the results of his experiments. The animal that lived longest lived for nine days.

The most recent and significant work on the problem has been done by Ivy and his associates.[15] They removed the stomach from fourteen dogs, and observed the animals for periods of six months to seven years. However, the stomach was removed completely from only three of the dogs. In the other operations a closed pouch was made of the stomach, thus removing the viscus physiologically. The operations were done in one stage with a relatively low mortality. The duodenum was anastomosed to the œsophagus by the end-to-side method. These investigators found that gastrectomized dogs, if properly fed, were maintained surprisingly well. Spontaneous anæmia developed in three of the fourteen dogs with absolute achylia gastrica on a diet which was adequate for normal dogs. Pregnancy uniformly induced anæmia (three times in one dog, one time each in two dogs). Ivy and his

associates[15] believe the achlorhydria was a predisposing factor for the development of anæmia in that it reduced the factor of safety of digestion.

Clinically, the operation of total gastrectomy is now generally accepted as definitely indicated in certain conditions. Apparently it was first attempted on a human being by Conner[7] when gastric surgery was in an early stage of development, and even the operation of partial gastrectomy was considered unjustifiable by many surgeons. Since Conner's patient died in the course of the operation, it is not to be wondered at that many years intervened before the operation was again attempted. Schlatter[22] reported the second case which was successful; the patient lived fourteen months after complete removal of the stomach for carcinoma. Exhaustive reviews of all the cases of total gastrectomy in human beings have been made by Uhlhorn,[24] and by Finney and Rienhoff.[10] They showed, as did Moynihan,[18] that many of the operations previously recorded as total gastrectomy were only subtotal excisions. Stahnke,[23] Judd, and Marshall,[16] Breitenback,[2] Flint,[11] Walters,[26] and Poole, and Foster[19] have since reported cases. In one of the cases reported by Moynihan,[18] anæmia developed after removal of the stomach. The case reported by Hartman[13] was suggestive of pernicious anæmia. Other similar cases have been reported, the most recent by Poole and Foster.[19]

Methods of experiments.—Dogs were used for all our experiments. Operations were carried out under ether anæsthesia, and with sterile technic. In the earlier experiments gastrectomy was performed according to the method of previous investigators. Our results were complicated by the same error noted in most of the previous investigations, that is, all of the stomach was not removed. It is relatively easy to remove all of the stomach of a dog, except a narrow rim of the cardia, but total gastrectomy is difficult. The reasons for this are: (1) The transition between œsophageal mucosa and cardiac mucosa usually occurs so near the line of attachment of the diaphragm around the œsophagus that when all of the stomach is removed the pleural cavity must be entered to secure sufficient length of œsophagus to suture; fatal infection of the pleura almost always occurs; (2) the blood supply to the lower end of the œsophagus and thus to the line of suture is scanty,[20] and, furthermore, the main arteries of this segment are sectioned in removing the stomach; (3) the œsophagus is not supplied with true serosa; (4) action of the diaphragm tends to separate the sutures; (5) the weight of the anastomosed duodenum on jejunum also tends to pull the suture line apart, and (6) as pointed out in a previous article on surgery of the œsophagus by Saint, and Mann,[21] operative procedures on the œsophagus do not inhibit peristalsis, and the frequent act of swallowing keeps the suture line on a more or less constant strain.

As noted in our earlier experiments, a small amount of cardia was almost invariably found at necropsy. In some experiments this tissue, which had been ignored at operation, had become enlarged and distended so that at necropsy several years after operation, the gastric cavity would contain 100 to 200 cubic centimetres of fluid (Protocol I).

After having made observations extending over several years on animals that were supposedly gastrectomized, only to find that a small portion of the cardia remained (Protocol II), a technic was developed which permitted the successful removal of all gastric tissue. This technic is similar in purpose but different in execution to that described by Heuer, Andrus, and Bell[14] for removal of carcinoma of the cardia. Briefly, the operative technic and post-operative treatment which overcome the difficulty of total gastrectomy in the dog are as follows:

FIG. 1.—Œsophageal-duodenal anastomosis secured sixty-five months and three days after operation. It may be noted: (1) Anastomosis is just caudal to attachment of diaphragm; (2) neither tube is dilated, and (3) the distance between the anastomosis and the opening of the common bile-duct is short.

The operation is carried out in two stages. In the first stage the diaphragmatic attachment to the œsophagus is cut away and as much of the œsophagus as possible is pulled into the abdominal cavity. The diaphragm is then sutured around the œsophagus. After permitting sufficient time for complete healing, the abdomen is again opened, the stomach is removed completely, and the duodenum is anastomosed end-to-end to the œsophagus. The animal is prevented from taking anything by mouth for a week. Fluid and food are supplied by the intravenous administration of a sodium chloride solution with glucose twice or more daily. In the second and third weeks after

operation, milk and syrup are given by mouth at frequent intervals. At the end of the third week, solid food can be given safely.

Following these procedures six animals were observed for periods varying from one and a half years to almost six years. The actual time the animals were observed after total removal of the stomach was, respectively, as follows: eighteen months, twenty-five months and four days, thirty-nine months and four days, forty-eight months, sixty-five months and three days (Fig. 1), and seventy months and twelve days (Protocol III).

We had intended originally to carry out several observations on these animals as regards possible changes in the constituents of the blood, and so forth. However, in view of the importance of the possible relation of gastric function to pernicious anæmia, it was determined not to complicate the experiments, but to make frequent blood counts and estimations of hæmoglobin, together with such general observations as could be made without detracting from the value of the main object of the experiment.

RESULTS.—*General observations*.—The animals always lost weight immediately after operation, which was to be expected in view of the fact that they were not given a maintenance diet until the end of the third week after operation. Within a few weeks after being given a generous diet they regained their weight. No change in their general condition could be attributed to the loss of the stomach; the changes that did occur were those which occur if dogs are maintained over long periods in the laboratory. It was found that a cereal mash cooked in the laboratory and fed as a routine to laboratory animals three times a week, was not tolerated very well by the animals without a stomach. Their diet consisted mostly of milk, syrup, horsemeat, and commercial dog biscuit. As the animals were kept indoors, cod-liver oil was given occasionally.

Because of our special interest in these experiments, we probably gave our animals more careful attention than other animals in the laboratory, although our intention was to attempt to maintain them under identical conditions. It was our impression that an animal without a stomach probably would not maintain itself as well as a normal animal under the normal conditions of a dog outside the laboratory. However, in the laboratory, a dog without a stomach was more easily maintained in good condition than an animal with greatly reduced hepatic tissue. No change in the hunger mechanism was noted. The gastrectomized animals would bolt their food like normal dogs. For the first few months after operation the dogs were fed three times a day, but later only once. At first there was a tendency to regurgitate food more frequently than by the normal dog, but even this was not noticeable after a year or so following gastrectomy.

Observations with the Röntgen-ray and barium meal showed that the food passed immediately from the œsophagus through the duodenum and jejunum into the ileum. The passage of the food from the œsophagus into the small intestine was so rapid that we were never able to obtain a picture that did

not have food in the jejunum even if only a small amount of food was given and the picture was taken immediately.

In none of the animals was there any dilatation of the duodenum. Consistent changes in either the size of the intestine or the thickness of the muscularis were not observed.

Observations on the erythrocytes and hæmoglobin.—Changes in the blood simulating pernicious anæmia did not occur. In most of the animals the erythrocyte count, the character, size, and so forth, of the erythrocytes and hæmoglobin, remained normal throughout the period of observation. In only two of the animals did secondary anæmia develop. In one of the animals the anæmia was due to continual bleeding from infectious sarcoma. In the other animal low intestinal obstruction developed which was associated with anæmia. We do not believe that the loss of gastric tissue was responsible for the anæmia of either animal.

Pigmentation of the intestine.—Only one positive observation was noted in the entire series of gastrectomized animals. After the stomach had been removed for a few months, it was observed that the entire small intestine became a dirty brown color. This pigment began at the suture line of the duodenum and œsophagus, and extended to the large intestine. The latter was only slightly involved. The discoloration was not due to the loss of the stomach from the body, but to the lack of gastric secretion in the intestine because it also occurs in loops of intestines in animals in which the gastric secretion is shunted away from certain portions of the intestine, but the biliary secretion is permitted to reach them. The color of the pigment fades quickly and only a small percentage survives the usual histological technic. It has therefore been difficult to determine its exact site. However, pigment has been observed in the histocytes in all of the histological structures of the intestine of the gastrectomized dogs, but the main portion of the pigment appears to be situated in the muscle cells of the muscularis.

Comment.—The results of these experiments require proper valuation. In general, they merely prove that a dog may live in good health under the condition of the experiment for more than half its normal life, without gastric tissue. In this respect the results of the investigation give more encouragement, if more is needed, for the total removal of the stomach in the human being when such procedure is indicated. However, our results do not necessarily disprove a relation between loss of gastric function and anæmia. They do show that if such a relationship exists in the dog, this species is capable of compensation for the loss of stomach to a remarkable degree.

Simple removal of the stomach of the dog probably will not elucidate the relationship between gastric function and pernicious anæmia as indicated by studies of man. A more hopeful appearing method of investigation would be to place the totally gastrectomized animal under physiological stress, as Ivy[15] is doing in his studies of pregnant gastrectomized dogs. But even the consistent development of secondary anæmia of gastrectomized animals which are under physiological stress, important as it is, should not be considered

as experimental proof of a relationship between loss of gastric function and pernicious anæmia. Only the experimental production of the characteristics of pernicious anæmia will suffice. Finally, it should be noted that since pernicious anæmia has never been observed in the dog, it may not be possible to produce such a type of anæmia in this species.

Summary.—A method for the total removal of the stomach of the dog was developed. All gastric tissue was successfully removed from six animals, and they were observed for periods varying for eighteen months to almost six years. Anæmia which could be ascribed to loss of gastric tissue did not develop in any of the animals.

PROTOCOL I.—*Dilatation of a small remnant of stomach.*—May 16, 1923, all of the stomach of an adult female dog, weighing 8.7 kilograms, was removed except a tube along the lesser curvature about the diameter of the œsophagus connecting the latter to the pylorus. The animal's erythrocytes and hæmoglobin were normal before operation and remained so after operation.

June 6, 1923, the weight of the animal was 8.4 kilograms. All of what was considered to be the remaining portion of the stomach was resected. The jejunum was sectioned, the distal end anastomosed to the œsophagus, and the proximal end was anastomosed to the ileum. The animal remained in good condition, maintained its weight, and the erythrocytes and hæmoglobin remained normal. Studies with a barium meal shortly after the second operation showed a small, dilated pouch which appeared to be a small remnant of stomach. Repeated observations with the barium meal demonstrated that this pouch was enlarging.

April 6, 1925, the weight was 8.5 kilograms. Exploratory operation disclosed a dilated pouch of the stomach which contained from 100 to 150 cubic centimetres of fluid. The animal was kept under observation. The pouch finally enlarged until it contained more than 200 cubic centimetres of fluid. The animal remained in excellent condition with normal weight, and normal erythrocyte count and hæmoglobin until November, 1929, when it began to lose weight and the number of erythrocytes decreased. The animal now appeared old. It had lost almost all its teeth.

January 12, 1930, the animal died suddenly. The cause of death could not be determined. The remaining portion of stomach had a capacity of 200 cubic centimetres of fluid.

PROTOCOL II.—*Difficulty of complete resection of the stomach of the dog.*—July 16, 1923, the stomach of an adult male dog, weighing 8.4 kilograms, was resected and the end of the duodenum was turned in. The first portion of the jejunum was sectioned, the distal end was anastomosed to the œsophagus and the proximal end to the ileum. The œsophageal jejunal anastomosis was against the diaphragm and could not have been placed any higher without entering the thorax. It could not be definitely ascertained by examination of the stomach whether all the cardia had been removed. The animal remained in good condition, and maintained its weight. The erythrocyte count and hæmoglobin remained normal, as before operation.

August 29, 1924, colitis which was prevalent in the laboratory at that time developed in the animal, and it was bled to death under ether. All organs were normal except the colon. A rim of cardiac mucosa less than 1 centimetre wide completely surrounding the intestinal tube had been left. This animal is not included in the series in which total gastrectomy was done.

PROTOCOL III.—*Complete removal of the stomach with subsequent long survival of the animal in apparently normal condition.*—May 18, 1925, a first-stage gastrectomy was performed on an adult male dog, weighing 10.4 kilograms. The vasa brevia were cut and ligated; the œsophagus was separated from the attachment of the diaphragm and after pulling as much of it as possible into the peritoneal cavity, the rent was repaired

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in the diaphragm. Repeated examinations before operation had shown the number of erythrocytes and hæmoglobin to be normal. The average number of erythrocytes was 5,400,000; the hæmoglobin was 80 per cent.

June 17, 1925, the animal remained in good condition. The erythrocytes and the hæmoglobin remained normal. The stomach was removed. The duodenum was anastomosed end-to-end to the œsophagus. Examination of the removed stomach showed conclusively that all of the viscus had been removed. Recovery from the operation was uneventful. During the first week after operation glucose in hypertonic sodium chloride solution was given intravenously. During the subsequent two weeks milk and syrup were given. The animal was then permitted to eat what it desired from the kennel ration. It lost some weight after the operation, which was subsequently regained. It remained in excellent condition for almost six years. During this time it was under constant observation. Blood counts and hæmoglobin estimation were taken weekly or bi-monthly. Repeated Röntgen-ray examinations with the barium meal were made. The weight of the animal remained above normal throughout the period of observation. It exhibited a tendency to get too fat at times so that a reduction of food was occasionally necessary. The fluctuations in weight from 10 to 16 kilograms were due to this variation in food intake. For months at a time the weight remained between 12 and 14 kilograms. In January, 1930, the animal began to look a little ragged and a small amount of cod-liver oil was given with its food for a few months. Owing to the loss of teeth because of age, it could not take its food as well as usual.

During the more than five years between the full recovery of the animal from the operation and within four months before it was killed, the number of erythrocytes varied between 4,400,000 and 6,400,000. The percentage of hæmoglobin varied between 75 and 100. The variation in estimation of hæmoglobin was partially due to changes in the method of estimation, as four different methods were used during the years the animal was under observation. During the four months preceding the animal's coming to necropsy, both the erythrocyte count and hæmoglobin remained a little lower than in the preceding years, although the former never went below 4,000,000 or the latter below 70 per cent. The erythrocyte count at the time the animal was killed was 4,360,000 and the hæmoglobin was 80 per cent. At no time was either below normal for the dog. The animal did not exhibit any illness until two days before it was killed.

April 27, 1931, the animal was noted quiet, which was in marked contrast to its usual manner.

April 29, 1931, the animal was very quiet and sleepy, and refused food. The urine was turbid and coffee colored. The animal was bled to death under ether, and necropsy was performed at once. The animal was in good physical condition; its weight was 12.4 kilograms. A layer of subcutaneous fat about 1 centimetre thick covered the entire body. The few remaining teeth were badly worn. The gastro-intestinal tract was normal except for the absence of the stomach, and a brownish-pink discoloration of the entire small intestine and to a large extent the colon. The line of anastomosis between the duodenum and œsophagus was in good condition; there was no stenosis or dilatation of duodenum or œsophagus. The gall-bladder was markedly distended with dark-colored bile. The urinary bladder contained a few cubic centimetres of a coffee-colored fluid. On the base of the bladder on the dorsal surface was a large, ulcerated area measuring approximately 2 centimetres in diameter. The base of this area was hard and indurated. The origin of the blood in the urine was evidently from the mucosa. All other organs, including the spinal cord, were grossly and microscopically normal.

BIBLIOGRAPHY

[1] Bettmann: Quoted by Unger, Ernst: Ueber totale Entfernung des Magens. Deutsch. med. Wchnschr., vol. xxxix, pp. 500–502, March 13, 1913.

[2] Breitenback, G.: Stoffwechselversuch nach totaler Magenresektion. München. med. Wchnschr., vol. lxxvi, pp. 1920–1921, November 15, 1929.

[3] Carrel, A., Myer, G. M., and Levene, P. A.: The Influence of the Removal of Fragments of the Gastro-intestinal Tract on the Character of Nitrogen Metabolism. III. The Excision of the Stomach. Am. Jour. Physiol., vol. xxvi, pp. 369–380, September, 1910.

[4] Carvallo, J., and Pachon, V.: Recherches sur la digestion chez un chien sans estomac. Arch. de physiol. norm. et path., vol. vi, pp. 106–112, 1894.

[5] Carvallo, J., and Pachon, V.: De l'extirpation totale de l'estomac. Arch. de physiol. norm. et path., vol. vii, pp. 349–355, 1895.

[6] Castle, W. B., and Locke, E. A.: Observations and Etiological Relationship of Achylia Gastrica to Pernicious Anæmia. Jour. Clin. Investigation, vol. vi, pp. 2–3, August, 1928.

[7] Conner, P. S.: Cancer of the Stomach; Gastrostomy; Gastroenterostomy. Med. News, vol. xlv, p. 578, November 22, 1884.

[8] Czerny, V., and Kaiser, F. F.: Beitrage operativen Chirurgie, pp. 83-160, 1878.

[9] Farrell, J. J., and Ivy, A. C.: Studies on the Motility of the Transplanted Gastric Pouch. Am. Jour. Physiol., vol. lxxvi, pp. 227–228, April, 1926.

[10] Finney, J. M. T., and Rienhoff, W. F., Jr.: Total Gastrectomy. Arch. Surg., vol. xviii, pp. 140–162, January, 1929.

[11] Flint, E. R.: Complete Gastrectomy for Carcinoma of the Stomach. Brit. Med. Jour., vol. ii, pp. 979–980, December 1, 1928.

[12] Grohé, B.: Die totale Magenexstirpation bei Thieren. Arch. f. exper. Path. u. Pharmakol., vol. xlix, pp. 114–122, April, 1903.

[13] Hartman, H. R.: Blood Changes in a Gastrectomized Patient Simulating Those in Pernicious Anæmia. Am. Jour. Med. Sci., vol. clxii, pp. 201–206, August, 1921.

[14] Heuer, G. J., Andrus, W. D. W., and Bell, H. G.: The Experimental Transplantation of the Diaphragm as an Adjunct in the Treatment of Lesions of the Lower End of the Œsophagus. ANNALS OF SURGERY, vol. lxxxi, pp. 273–286, January, 1925.

[15] Ivy, A. C., Morgan, J. E., and Farrell, J. J.: The Effects of Total Gastrectomy. Experimental Achylia Gastrica in Dogs with the Occurrence of a Spontaneous Anæmia and Anæmia of Pregnancy. Surg., Gynec., and Obstet. (In press: Manuscript read by the courtesy of the senior author.)

[16] Judd, E. S., and Marshall, J. M.: Total Gastrectomy with Report of a Successful Case. Surg., Gynec., and Obstet., vol. l, pp. 1008–1011, June, 1930.

[17] Monari, Umberto: Experimentelle Untersuchungen über die Abtragung des Magens und Dünndarms beim Hunde. Beitr. z. klin. Chir., vol. xvi, pp. 479–492, June, 1886.

[18] Moynihan, B. G. A.: A Case of Complete Gastrectomy. Lancet, vol. ii, pp. 430–431, August 12, 1911.

[19] Poole, A. K., and Foster, L. C.: Chronic Syphilitic (?) Gastritis with Total Gastrectomy and Pernicious Anæmia. Jour. Am. Med. Assn., vol. xcvi, pp. 2187–2190, June 27, 1931.

[20] Saint, J. H.: Surgery of the Œsophagus. Arch. Surg., vol. xix, pp. 53–128, July, 1929.

[21] Saint, J. H., and Mann, F. C.: Experimental Surgery of the Œsophagus. Arch. Surg., vol. xviii, pp. 2324–2338, June, 1929.

[22] Schlatter, Carl: Ueber Ernährung und Verdauung nach vollständiger Entfernung des Magens-Oesophagoenterostomie—beim Menschen. Beitr. z. klin. Chir., vol. xix, pp. 757–776, 1897.

[23] Stahnke, E. N.: Ein Fall von totaler Magenresektion. Deutsch. Ztschr. f. Chir., vol. ccxi, pp. 408–410, 1928.

[24] Uhlhorn, Emma: Totale Exstirpationen des Magens. Arch. f. klin. Chir., vol. cxliv, pp. 593–611, 1927.

[25] Verson, S.: Gastrectomia totale transtoraccia nel cane. Arch. per le sc. med., vol. xxxvii, pp. 42–57, 1913.

[26] Walters, Waltman: Physiological and Chemical Studies Following Successful Total Gastrectomy for Carcinoma. Jour. Am. Med. Assn., vol. xcv, pp. 102-106, July 12, 1930.

CARCINOMA IN THE DUODENUM

ORIGINATING FROM ABERRANT PANCREATIC CELLS

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Carcinoma occurring in the duodenum is an unusual condition.

Carcinoma found in the duodenum proven to have originated from misplaced pancreatic cells is very rare, a fairly careful search of the literature having revealed but one somewhat similar case in which the site of the new growth was at the pylorus and involving the stomach wall as well as the duodenum.

The first case of duodenal malignancy was reported by Hamburger, in 1746. His case had a carcinoma situated in the first portion which perforated; a fatal peritonitis followed. Jefferson collected reports of 109,201 autopsies from English, German, American and Swiss hospitals and found only forty-three cases of carcinoma of the duodenum or about .04 per cent. A statement of interest and fact is made by this author to the effect that "inch for inch the duodenum is more likely to undergo carcinomatous change than the jejunum or ileum," so that, rare as a malignant neoplasm is in the proximal end of the small bowel, it is still more rare in its distal portion.

Most of the cases of carcinoma of the duodenum reported seemingly spring from the cells of the lining mucosa and fewer from Brunner's glands; many of these cases having the history of a long-standing ulcer with ensuing malignant degeneration. The possibility of aberrant pancreatic cells being a point of origin is hinted at by many authors, but proof as to its actual occurrence is usually lacking. Bland-Sutton rather belittles this idea when he states "a consideration of tumors of the small intestine would be incomplete without reference to the suggestion that cancer of the small intestine may arise in an accessory pancreas—it is necessary to mention accessory pancreas when considering cancer of the duodenum and small intestine because those pathologists who still believe that carcinoma arises in embryonic vestiges think it probable that this perversion may arise in islands of pancreatic tissue. There is no evidence to support this theory nor that which attributes duodenal cancer to morbid changes in Brunner's glands." The actual incidence of a malignant change taking place in a duodenal ulcer is a point that is still *sub judice*.

Ewing classifies carcinoma of the duodenum as follows:

(1) Carcinoma following ulcer; similar to pyloric ulcero-carcinoma which leads to stenosis and adhesions and in which class metastases are frequent and widespread.

(2) Carcinoma found about the papilla of Vater; in which group jaundice

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of sour eructations or vomiting. Never noticed that her stools were dark. Has been afraid to eat meat because she claims that this aggravates the pain. Appetite fair. Bowels occasionally constipated and diarrhœa rarely. No urinary symptoms. Menses regular. Married nine months. Perspires very freely at night. Has lost ten pounds in the last four weeks. Feels weak and is easily fatigued. The pain in the lumbo-sacral region has been annoying her for the past two weeks and has been increasing in severity. This pain is across her back and seems to radiate down her left thigh.

The patient does not look acutely ill. No cervical or axillary adenopathy.

Palpation of the abdomen reveals no masses. There is a sense of resistance, half of the abdomen more marked on the right side than the left. Radioscopic examination of the pelvis discloses arthritic changes involving both sacro-iliac synchondroses with slight broadening of the right.

Fluroscopic examination shows the stomach to be "J" shaped, normal in contour and moderately ptosed. Duodenal bulb is incompletely filled. The first portion of the basal region of the cap shows a circumscribed clear shadow due to displacement of some barium. A re-examination shows this same filling defect. Six hour film showed no gastric residue. Head of opaque meal at the hepatic flexure, tail in terminal ileum. There are a few flakes of barium in the first portion of the duodenum. Films taken at these examinations reveal the same findings as the fluroscopy.

Conclusions.—Combined radioscopic and fluroscopic examination of the upper gastro-intestinal tract disclose the presence of an organic lesion in the first portion of the duodenum the characteristics of which suggest that the lesion is probably a benignant tumor, such as a polyp. Gastric extraction, free HCl, o; total HCl, 17.

Urine, blood, sputum and examinations negative.

Operation September 30, 1930. Gas-oxygen-ether anæsthesia. Upper right rectus incision. No free fluid found on opening the peritoneal cavity. In the first portion of the duodenum and within the first inch of this structure there is a small mass palpable within the wall of the bowel. This is circular in outline and about one and a quarter centimetres in diameter. Seems to be firmly attached to the duodenal wall at its anterio-inferior aspect. Just below this structure there is some puckering of the peritoneum on the duodenal wall which extends downward toward the pancreas. The duodenum can be lifted well away from the pancreas and an artificial mesentery created by traction; this artificial structure contains no glands and is very thin.

In order to examine the tumor more thoroughly an incision was made in the normal duodenal wall and lengthened so as to include the pylorus and some of the stomach wall. The tumor was now turned out through this incision and found to be a smooth, disc-like structure about a half centimetre in thickness. It was covered with mucous membrane which was not ulcerated. The mass itself was firmly embedded in the duodenal wall and was practically immobile. The mass seemed hard and did not fluctuate. The tumor was excised by a circular incision well away from its margins. During this procedure the mass, which was a cyst, ruptured. The walls of the cyst were about one quarter centimetre in thickness and it had a smooth-lined cavity. The fluid which escaped into the protecting laparotomy pads was light brown in color and contained some brown, dustlike particles.

The rent made by the excision of the tumor was closed, as was the incision made in the bowel to inspect the tumor. The duodenum, as the result of this suturing, seemed somewhat narrowed, so a gastrojejunostomy was made. No glands were palpated at any time. Abdomen closed.

Microscopic section of the material removed shows mucosa infiltrated with numerous red blood-cells which have formed a rather thick layer on the surface and extend down between the glandular elements to the submucosa. The muscularis is normal but in the outer coat of the latter are numerous discrete and confluent islands composed of simple acini bound together with small strands of connective tissue. These islands or nests resemble the normal pancreatic tissue but there are no islands of

Langerhans. In some areas there is breaking through of the muscle fibres and the cells of the acini mentioned are growing in a wild disordered manner. The serosa is infiltrated and covered with blood.

Diagnosis.—Carcinoma of the duodenum; probably secondary to pancreatic rest.

The only other case that approaches the pathologic aspects of this case is the one reported by Branham. This case is cited by Deaver and Ravdin as having been published in 1913, Jefferson giving the date as 1903. It appeared, however, in the Maryland Medical Journal in 1908. Branham's case is one of a growth at the pylorus involving the stomach wall as well as the first portion of the duodenum. A pylorectomy was performed. The sections were seen and attested to by Welch as originating from pancreatic tissue. Patient was reported well and free from symptoms nine years later.

A point of great diagnostic significance is gleaned from many reported histories of cases of carcinoma of the duodenum, *i.e.,* the stomach analysis in a very large number shows a very low acidity or complete absence of free hydrochloric acid; this obtained in our case. The importance of this sign is that, given a case which clinically may be considered one of ulcer, and the gastric analysis shows a lowered or totally deficient acid content, the diagnosis of a carcinoma must be well considered and a good X-ray examination made to complete the picture for diagnosis previous to a radical restriction of the ulcer.

In this case a malignancy was not suspected and it was not until the pathologic report was returned that the true nature of the condition was disclosed. A sub-total resection of the duodenum and adjacent stomach might have been made at the time had the real state of affairs been known, or suspected but the patient left the hospital and only consented to remain under observation by her family physician, who has reported a marked gain in weight and strength.

REFERENCES

Jefferson: Brit. Jour. Surg., vol. iv, p. 109, 1916–1917.

Orth: Spec. Path., 1887.

Bland-Sutton: Lancet, vol. ii, p. 2; 931, 1914.

Ewing: Neoplastic Diseases, Third Edition.

Outerbridge: ANNALS OF SURGERY, vol. lvii, p. 57; 402, 1913.

Branham: Maryland Med. Jour., April, 1908.

Eusterman, Berkman, and Swan: ANNALS OF SURGERY, vol. lxxxii, p. 153, 1925.

Brill: Am. Jour. Med. Sci., vol. xxviii, p. 824, 1904.

Perry, and Shaw: Guys. Hosp. Reports, vol. l, p. 214, 1893.

Archibald: Ill. Med. Jour., vol. lvii, p. 62.

Deaver, and Ravdin: Am. Jour. Med. Sci., vol. clvi, p. 469.

McGuire, and Cornish: ANNALS OF SURGERY, vol. cxxii, p. 600, 1920.

Coupland: Trans. Path. Soc., vol. xxiv, p. London, 1873.

Dewis, and Morse: N. Eng. Jour. Med., vol. vii, p. 383.

Countryman: Trans. Chicago Path. Soc., vol. xiii, p. 140.

Geiser: Basel Theses, A. Pries, Leipzig, 1906.

Warmburg: E. Streisand, Berlin, 1891.

Colp, and Cohen: Surg. Gynec. and Obs., vol. iii, p. 45, 1927.

Aronson: C. Siebert, Berlin, 1907.

Eloesser: Fälle von Pancreasser Krankungen. Mitt. Grensgeb. d. Med. 7. Chirurg., vol. cxcv, p. 18, 1907.

BRIEF COMMUNICATIONS
CARCINOMA OF THE HEPATIC DUCT

Wylegschani[1] was able to collect a total of thirty-four cases of primary carcinoma of the hepatic duct in the literature and adding one additional case brought the total to thirty-five. Since 1927 one case has been added.[2]

This group of carcinomas are slow to metastasize. To some extent this is probably the result of early fatal secondary injury by biliary obstruction. They are generally adenocarcinomas which occasionally display a predominance of fibrous reaction (scirrhous type). The largest reported (Wylegschani) was the size of a pigeon's egg. Biliary obstruction, with obstructive jaundice progressive in type, and death from cholæmia and liver insufficiency, and finding of dilated bile-ducts above the obstruction are common. Portal cirrhosis is an occasional concomitant finding as are gall-stones. The gall-bladder and ducts below the tumor are usually contracted although in Wylegschani's case the gall-bladder and common duct were distended with blood-stained mucoid fluid.

A white male, fifty-three years of age, was admitted to the Research and Educational Hospitals on the medical service of Dr. C. S. Williamson, July 8, 1931, complaining of progressive jaundice, six weeks' duration, and weakness for the same period of time associated with a loss of 22 pounds. He stated he had been suffering from stomach trouble, characterized especially by distension and discomfort after meals, for a period of five years.

Eight weeks prior to admission he noticed that his urine was extremely dark and shortly thereafter he noticed jaundice of the skin and a severe sharp pain in the epigastrium radiating posteriorly to the mid-scapular region. The episgastric pain disappeared spontaneously in a few days, but the pain in the back persisted to the day of admission. Four of five clay-colored stools a day were noted and progressive weakness complained of. His appetite has been good, although he abstained from meats and fats because he noted increasing darkening of the urine following these foods. A light-brown stool was said to have been passed a few days before admission.

On physical examination a marked jaundice was noted and the loss of weight was apparent. Neither the liver nor the spleen was palpable, although the abdominal examination was not entirely satisfactory because of poor coöperation. The stools were clay-colored with chemical blood demonstrable. The blood sugar was 86, the icterus index 117. Bile was present in the urine in large quantities. The white count was 13,850 with 83 per cent polymorphonuclears.

After suitable pre-operative preparation and with a diagnosis of obstructive jaundice on the basis of the carcinoma of the head of the pancreas, an exploratory laparotomy was undertaken on the 23d of July by one of us. (Dr. J. D. Koucky.)

At this time the gall-bladder was found to be markedly distended as was the common duct. On opening the latter, it and the gall-bladder were found to be filled with white bile. The entire length of the common duct, including the opening into the duodenum, was widely patent and free from obstruction. On palpating the hepatic duct, however, a

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[1] Frank Furter, Zeitschrift für Pathologie, vol. xxxv, pp. 417–433, 1927.

[2] Vander Veer, Edgar A., and Nelms, H., Annals of Surgery, vol. lxxxvii, pp. 157-159, 1928.

rather poorly localized indurated area was found near the exit from the liver, in which region the duct was found to be obstructed on exploration with a probe. The stricture was dilated with a curved forceps and a small amount of tissue was removed with a curette. A small amount of white bile was obtained from the duct above the stricture. A catheter was placed in the bile-ducts from a point above the tumor through the ampulla. The duct was closed.

The patient was returned to the ward in good condition, and in the next two days complained of little pain but vomited large amounts of dark-brown material.

On the 26th of July vomiting became more persistent, pulse became weaker, and on the 27th, after a period of hiccoughing and marked vomiting, the patient died. The temperature at no time exceeded 100.4.°

At autopsy an area of consolidation 2 centimetres in diameter was found in the right pulmonary lobe. The myocardium showed moderate evidences of degeneration and the kidneys showed the usual picture of cholæmic nephrosis. The stomach was dilated and filled with very dark-brown fluid, about 1,500 cubic centimetres in amount. A rubber catheter was found free in the ileum. The liver weighed 1,800 grams; the surface was granular, dark green, the consistency firm, and the cut surface was deeply bile-stained with dense, gray-green, trabecular markings and intervening islets of proliferating parenchyma tissue.

There was a tumor of the hepatic duct about 1 centimetre from the origin in the liver measuring about 2 centimetres in length, and about 1½ centimetres in diameter. On opening the duct in this region it was found to be widely patent and the surface roughened. On cut section of the liver, the widely dilated bile-ducts were found filled with white mucoid, glistening material and here and there ½ to 1 millimetre-sized focal gray to yellow softened areas were seen.

The gall-bladder was markedly dilated and thin walled and contained about 200 cubic centimetres of the same white bile and the common bile-duct was widely dilated. The opening through the papilla of Vater measured 3 millimetres in diameter and above this point the duct was 5 millimetres in diameter. Except for the localized postoperative changes no other findings of note were present.

Microscopically, both the curettage specimen obtained at operation and the section of the tumor obtained at the autopsy revealed an adenocarcinoma of a low-grade malignancy.

In sections of the liver the parenchyma cells were moderate in size and generally well preserved. They contained a large amount of golden granular pigment. The Kupfer cells were prominent, swollen, and the majority of them filled with brown, coarsely granular pigment. The periportal connective tissue was markedly increased in amount and the seat of a pronounced round-cell infiltration; in focal areas abscesses of miliary type, made up of polymorphonuclears with little connective tissue, were prominent. Sections of the gall-bladder and common duct revealed atrophy of the muscular elements in the markedly thinned-out wall and showed no inflammatory changes.

Important features to be emphasized in this case are: first, the recording of an additional primary carcinoma of the hepatic duct in literature; second, the unique method of surgical attack employed for treatment and diagnosis, namely, dilatation and curettage of the hepatic duct; and finally, the changes noted above and below the point of obstruction and certain physiological aberrations connected with these changes.

The fact that bile was found in the Kupfer cells emphasizes the independent rôle of excretion from that of the formation of bile; and the failure of restoration of this function following long-continued obstruction can be explained only on the basis of the effect of the long-continued pressure on the excretory function of the liver cells. The short period of time between

the relief of obstruction and the death of the patient, namely, four days, is not long enough to entirely evaluate this factor. However, it is apparent that the restoration of this function once lost must require a considerable period of time.

Finally, a marked dilatation of the gall-bladder by mucoid material, so-called white bile, and the similar dilatation of the common duct below the point of obstruction demands an explanation.

From a morphological standpoint, atrophy of the muscular elements was noted. The fact that these parts were filled with a mucoid material would indicate that bile in itself must offer an essential stimulus to the rhythmic emptying of the gall-bladder and the muscular contractions of the common duct.

In conclusion, there may be emphasized that there is apparent dissociation of the functions of formation and excretion of bile in so far as the liver is important. The abolition of the function of excretion resulted in this case from long-continued obstruction by a carcinoma of the hepatic duct. The relief of this obstruction for a period of four days was insufficient to allow restoration of the excretory function, a phenomenon not infrequently encountered following relief of any type of continued obstruction.

We should like to emphasize further the fact that mere distension of the gall-bladder by mucoid material was not sufficient, apparently, to induce that organ to empty itself; and as an apparent result of the lack of normal physiological stimulus, namely, the presence of bile, there was marked dilatation of both the gall-bladder and the common duct in the absence of any obstruction in either the cystic or the common ducts.

Summary.—(1) An additional carcinoma of the hepatic duct is added here to the thirty-six already recorded in the literature.

(2) A unique method of surgical diagnosis and treatment was resorted to, namely, dilatation and curettage of the hepatic duct.

(3) Emphasis is placed upon the failure of the liver to excrete bile during the four days following the operation.

(4) Marked dilatation of the gall-bladder and common duct are explained by the lack of bile, the physiological stimulus with the emptying of this organ.

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SUBUNGUAL MELANOMA IN NEGROES

MELANOTIC tumors of all types are very rare in the Negro. Adair, Pack, and Nicholson[1] in a review of the literature on this subject found fourteen reported cases up to 1926. One of three cases of subungual melanoma which these authors observed at Memorial Hospital occurred in a Negro. In 1927 Bauer[2] reported two cases of melanotic tumors occurring in Negroes, one of which was a subungual melanoma. We can now add a further case to those already reported.

A Negress, seventy-three years of age, came to the Cleveland Clinic complaining of discoloration of the fifth finger of the left hand. The following history was obtained: For twenty years she had had a "black spot" on the nail of the fifth finger of the left hand. This spot grew gradually larger and another developed, so that there were two large discolored areas on the nail, both quite black in color. This condition had remained constant for the past fifteen years, during which time the area of discoloration had not increased in size. Six months previous to the admission of the patient, the nail split, assuming a bifid character. Up to that time the nail had been normal in shape and configuration (Fig. 1).

Physical examination of the patient revealed nothing abnormal apart from the black discoloration of the fifth finger of the left hand, including the nail which was bifid due to a splitting down its centre as far as the nail bed. Pus could be evacuated from the central split down the nail. The palmar aspect of the tip of the finger presented an area of dark, gangrenous-appearing skin. No enlarged regional lymph-nodes could be detected.

Clinically, the lesion was thought to be an infected, melanotic, pigmented tumor, the exact pathological nature of which could not be determined. Microscopical examination of a small piece of tissue from the nail bed showed that the tumor was a subungual melanoma of low-grade malignancy.

Fig. 1.—Photograph of fifth finger of left hand, showing subungual melanoma.

The finger was amputated at the metacarpo-phalangeal joint and the head of the metacarpal bone was removed. The wound healed by first intention.

The following is the report of the microscopical examination of the removed tissue:

"Section of tissue through the nail bed shows thickened epidermis covered by a heavy layer of keratohyaline material in the region of the base of the nail. In the region of the tip, the epithelium is destroyed, the tissue is ulcerated, and in the deeper layers there is a large quantity of very cellular tissue rich in melanin pigment. In some areas the quantity of melanin pigment is large and the number of actively growing tumor cells is small. This is particularly true of the area near the base of the nail. Near the tip of the finger the tumor cells predominate over the pigment. The vast majority of the cells, however, contain fine, granular, dark-brown pigment in the cytoplasm. The tumor cells are quite large; some are multinucleated. Mitotic figures are rare" (Fig. 2).

Second Pathological Report.—"Longitudinal section through the distal phalanx, including the nail, soft tissues and bone—which has been decalcified—shows keratosis of the nail bed and ulceration of the tip of the finger. Considerable diffuse inflammatory reaction is present in the soft tissues. There is no involvement of bone. A large amount of melanin pigment may be observed below the epidermis under the tip of the nail. The melanin-forming cells show very little evidence of active growth."

The pathological diagnosis was *subungual melanoma* of low-grade malignancy. The

patient was instructed to return to the clinic at frequent intervals for examination but she neglected to do so. She was visited July 20, 1931, ten and a half months following the removal of the finger. The amputation scar was found to be in perfect condition and there was no evidence of any neoplastic process.

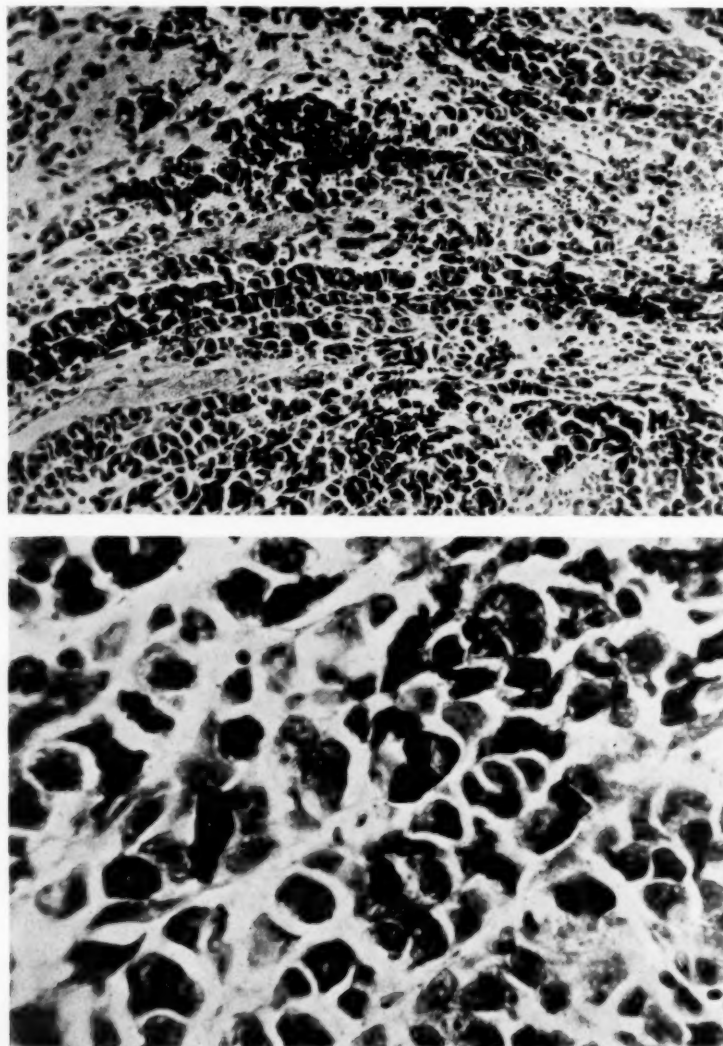The left epitrochlear and axillary lymph glands, however, were definitely enlarged

Fig. 2.—A—Photomicrograph of subungual melanoma (x 150). B—High-power photomicrograph of same area of tissue as shown in A (x 600).

and hard, but not fixed. The patient was in excellent condition and had not noticed the presence of the nodules in the left epitrochlear and axillary regions.

BIBLIOGRAPHY

[1] Adair, Frank E., and Pack, George T., with the assistance of Mary E. Nicholson: Mélanomes sous-ungueaux et leur diagnostic différencial. À propos de quatre cas. Laboratory studies vol. ii and Clinical studies vol. vii, from the Memorial Hospital, New York City, 1930.

² Bauer, John T.: Malignant Melanotic Tumors in the Negro. Arch. of Path. and Lab. Med., vol. iii, p. 151, 1927.

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ADRENAL NEUROBLASTOMA IN INFANCY—15 YEAR SURVIVAL

IN the Journal of Medical Research for May, 1917, vol. xxxvi, No. 2, I reported a case of adrenal tumor under the designation of neuroblastoma. This tumor had been removed by Dr. Willard Bartlett, of St. Louis, from an infant of eleven months. The tumor was a typical example of its type and relatively undifferentiated.

The following paragraph occurs in the original report: "This case is distinctive among undifferentiated tumors in one respect that deserves mention. It is the first case successfully operated upon. Although theoretically one cannot avoid the feeling that evidence of metastasis may occur, yet two and one-half months after operation the child's health continues to improve. All other cases that have come to operation have died during or shortly after the operative procedure." Since then other cases have been successfully operated on, including one in this clinic recently by Dr. William H. Goodwin.

The present note is made to put on record the fact that Doctor Bartlett's patient has survived for fifteen years. He has recently been seen by Doctor Bartlett who says that he is in perfect health.

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CANCER IN NEW YORK CITY

THE weekly bulletin of the Department of Health of the City of New York dated November 1, 1931, gives the following statistics as to cancer in New York City. With the permission of Dr. Shirley W. Wynne, Commissioner of Health, they are submitted herewith in the belief that they are of sufficient importance, by reason of their completeness and their extent, to warrant their introduction in any general review of the subject of cancer.

The New York City cancer committee is carrying on a campaign of education to call public attention to the menace of cancer and to rouse the people to an appreciation of the significant signs and symptoms which may indicate cancer in its early stages. Chief emphasis is laid on the importance of early diagnosis and on the danger attending failure to consult a qualified physician.

The number of deaths from cancer in New York City has steadily increased in recent years. From only 78 per 100,000 of population in 1910, the deaths have risen to 117 per 100,000 in 1930, an increase of 50 per cent. in the twenty years. The actual number of deaths in New York City from this cause in 1930 was 8,025.

This increase is due to several factors—more accurate statistics, better diagnosis, and greater average age reached by the population, which puts a larger number of people into the middle-age group, *i.e.*, the cancer age. The result of all these factors is that in 1930 the deaths from cancer in New York were outnumbered only by those from heart disease.

Unfortunately, since cancer is not a reportable disease, the available statistics cover only the mortality. The number of cases successfully treated cannot be computed. If all the facts were known, cancer would probably be found to be even more prevalent than is at present realized, but it would also be seen that by early discovery and prompt and proper treatment cures can be affected.

That cancer is becoming more important as a cause of death in New York is shown by comparing the leading causes of death in 1910 and in 1930. In 1910, pneumonia was the most frequent cause, with 220 deaths per 100,000 of population; pulmonary tuberculosis was second, with 182 deaths per 100,000, and heart disease third, with 144. Cancer was fifth on the list, causing 78 deaths per 100,000 of population during that year.

By 1930, however, cancer had risen to second place, with 117 per 100,000 of population, an increase of 50 per cent. Pneumonia, tuberculosis and nephritis, on the other hand, all showed marked decreases.

Although there are more men than women in New York City, the deaths from cancer among females exceed those among males. In 1930, this difference was more marked in the age groups between twenty-five and sixty-five. Before the age of twenty-five the difference was less, although the deaths of females were more frequent. After the age of sixty-five, the balance changed, more men than women dying from cancer, in spite of the fact that the total number of women living in that age group was considerably in excess of men.

In 1930 the female death rate was 122 per 100,000 as compared to 111 for males.

The stomach and the liver are the most frequent sites of fatal cancer. Last year, in New York City, there were 2,605 deaths from cancer of these organs, 1,429 in men and 1,176 in women. In addition, there occurred 1,435 deaths from cancer of the intestines and rectum, 704 in men and 731 in women, making a total of 4,040 deaths in both sexes due to cancer of parts of the digestive system.

Cancer of the breast and genital organs caused 1,841 deaths, by far the largest number, 1,610, occurring in women. Cancer of the kidneys and bladder, on the contrary, is more common among men, as are cancer of the lungs, cancer of the buccal cavity, and cancer of the skin.

Cancer of the skin caused 66 deaths among men and 40 deaths among women, most of which should have been prevented, as cancer of the skin is visible, accessible, and in its early stages usually curable by surgery or radiation. In these tumors the relation between chronic irritation and the development of the growth is very clearly shown, and it should be possible to prevent a large proportion of them.　　　　　LEWIS S. PILCHER.

BOOK REVIEWS

CANCER DU PANCREAS. By CH. OBERLING AND M. GUERIN. Octavo; pp. 363. Paris, Gaston Dion & Cie, 1931.

THIS volume on CANCER OF THE PANCREAS is the final volume of the series published under the direction of Professors Hartman and Berard, completing a series of ten volumes in which cancer of various regions of the body has been considered, those thus far treated being the intestines, the kidney and urinary passages, the rectum, the thyroid gland, the uterus, the visual apparatus, the œsophagus, the nasal passages and bones, thus forming a library of the highest value and most thorough and comprehensive character.

Of the series, this one devoted to the pancreas is peculiarly timely and important due to the obscure nature of the earlier symptoms of the disease, the difficulties of diagnosis and the apparent impossibility of satisfactory treatment. Dead-house statistics have given an average of three cancers of the pancreas to every 1,000 autopsies. As to its frequency in comparison with other malignant tumors, different observers differ in their estimations, from three to twenty-three per 1,000 of which figures the lowest are probably nearest the truth. As to sex, the percentage among men is almost double that among women. Although tumors of the pancreas had been recognized at various times, it was not until 1888 that the diagnosis of pancreatic cancer was placed upon a satisfactory basis by the researches of Bard and Pic. The present treatise brings our knowledge with regard to this seat of cancer fully up to date and must be considered as a valuable contribution to the subject.

In its normal state, the pancreas does not lend itself to abdominal palpation. Of all the organs of the abdominal cavity, it is the most fixed. The head is especially difficult of mobilization. Its secretion is double in its function; internally discharging into the blood a substance without which the organism cannot make use of glucose; externally when emptied into the duodenum as a pancreatic juice, it exerts specific digestive influences upon fats, hydrocarbons and proteins. As to the development of cancer within its substance, it is not free from the conditions in other parts of the body in which the development of cancers is well understood to be preceded by chronic inflammatory conditions. The authors make the general statement that the first question which has to be settled in cases of cancer of the pancreas is by what chronic inflammatory lesion has it been preceded, what has been the origin of the chronic pancreatitis which has now become complicated with cancer? The intimate relation between the pancreatic ducts and the excretory ducts of the liver and the gall-bladder must inevitably obscure the pancreatic involvement by the preceding and major biliary symptoms. The natural

result is that cancer of the head is much more frequent, from 70 to 80 per cent. of all cases belonging to that class. Later, however, the symptoms due to the pancreatic tumor dominate the scene, although the gall-bladder may be largely distended and the liver enlarged. In the later history of cancers of the head, the organs situated in the epigastrium, namely, the liver, the duodenum, the stomach, and the transverse colon, are all bound together with the pancreas by numerous adhesions which solidly fix the mass to the posterior wall of the abdomen. Cancers of the body invade very rapidly the retro-pancreatic connective tissue involving especially the vessels and nerves. Involvement of the portal vein is frequent. Considerable contractions of the aorta and vena cava may be produced, branches of the celiac plexus become compromised and atrophy. The predominance of ascitic infections and crises of pain are the special accompaniments of this form. The cancer, wherever it may primarily be localized, extends often to the neighboring parts of the organ, even to its totality. Secondary alterations from necrosis and hæmorrhages are frequent. The formation of extensive adhesions takes place early. The tumor becomes attached and fixed more and more in the pre-vertebral plane, the stomach is almost always involved in the adhesions. The duodenum is habitually solidly fixed, the gall-bladder, the transverse colon and certain parts of the small intestine may be involved in the adhesions. Metastases are almost constant in the regional ganglia and in the liver, more rarely in the lung.

The pancreatic cancer may be of secondary origin as a direct propagation from a malignant tumor of the neighborhood. Cancer of the pancreas is essentially, in its earlier development, a latent process. One sign, however, belongs properly to it, namely, intense and rapid denutrition. Later, various symptoms arise from its extension due to compression and invasion of neighboring organs. Jaundice, which accompanies cancer of the head of the pancreas, is very light at first, gradually progressing until it attains an extraordinary intensity. A persistent diarrhœa associated with jaundice always awakens the suspicion of cancer of the head of the pancreas. The failure to digest fats is a well-known sign. Emaciation is intense and rapid. It is rare to be able to perceive any tumor by palpation. The disease progresses continuously, the digestive troubles increase, the emaciation becomes more accentuated, the fatal end supervenes at the end of a few months, possibly accelerated by such accidents as hæmorrhages, cardiac failure and pleuropulmonary affections. The pain which is a capital symptom of cancer of the body of the pancreas is felt most frequently in the epigastric region. Often it radiates to the back or even to the iliac region. This pain comes on almost always in the form of crises which supervene apparently without cause. They are of short duration but of frequent repetition. The digestive symptoms are frequent and intense, including anorexia, repugnance to fatty matter, frequent vomiting. The symptoms of cancer located in different sections of the pancreas are often so complicated in their manifestations as not to fall

under any one form of classification. Sometimes when the symptoms may correspond to one of the forms, the autopsy will demonstrate a different location. Atypical forms are also met with in cases differing totally from the classical forms. Thus, the symptoms due to digestive troubles, enlargement of the liver, ascites, vary to a degree that may suggest other organs as the seat of the disease rather than the pancreas. A very marked glycosuria may be present. Gastro-intestinal symptoms sometimes predominate; ascites may take on considerable proportions, becoming the chief manifestation; a renal syndrome may be supreme. In some cases, the pancreatic symptoms are so latent as to escape detection until an intercurrent disease has occasioned autopsy.

After these observations as to the symptoms and effects of the disease, it is to be expected that the consideration of diagnosis might receive considerable discussion. To the subject of diagnosis over forty pages are devoted. Quite a minute analysis is given of the various functional as well as symptomatic conditions that the various forms of the affection may present.

Concerning the subject of treatment, the efforts which have been made to the surgery of these conditions are considered at some length. For the last half century the efforts of treatment have been directed along the line of surgery, notwithstanding that anatomical conditions are such as to render operative interference so very difficult. Numerous experimenters have been able to practice partial and even complete ablations of the pancreas in the dog. In man the total removal of the pancreas, even if operatively possible, should be interdicted, because of the fatal diabetes which would follow such removal. It is agreed among surgeons that ablations should not exceed 50 per cent. of the total bulk of the gland. The operative difficulties will vary according to the segment of the pancreas with which the operator has to deal. The removal of the tail and of the body are relatively easy. The head, however, is deeply fixed posteriorly and encircled by the duodenum, covered by the root of the transverse mesocolon and involved among important blood-vessels. Its removal is not only laborious and delicate but involves the section of part of the duodenum and division of the ductus choledochus and the canal of Wirsung. The disposition of the fluids of these canals is always a problem involved. Perfect asepsis is absolutely necessary with careful toilet of the abdominal cavity and the operative field. Various methods of operative technic are described and fully illustrated by a series of plates.

Extracts from literature are given, containing the operative results obtained by many surgeons. Records of partial pancreatectomy are available in more than twenty-five cases. These show that while an operative attack more or less radical may be possible, thus far in all cases ultimate death has followed from recurrent disease. Thus, in two cases of duodenopancreatectomy which are given, in one case operative recovery took place but death on the twenty-fourth day thereafter followed from glycosuric cachexia. In the second case, the operator was unable to complete the opera-

tion and made a second attempt later, at which time the patient died of the operative shock. This statement, however, is modified by the remark that the totality of the resection is very doubtful in these cases. The first case is believed to be one done by Billroth in 1882, but its details are so defective that the case remains doubtful. In the second case, a woman, sixty-eight years of age, the surgeon (Franke) is stated to have taken away the entire gland, a small supernumerary pancreas, however, having been left behind. The patient suffered from glycosuria for three weeks post-operative, and finally succumbed to a general cancerous diffusion five months later. In cases where cancer is very extensive and there are present also metastases in the liver or elsewhere, palliative treatment alone is practicable. One author (Swain) estimates that scarcely 4 per cent. of pancreatic cancers when detected are limited enough to justify efforts at their total removal. Heiberg, basing his opinion upon thirty-five personal cases, claims that metastases exist almost always at the time of intervention. Palliative operations may be required by intestinal obstruction or biliary retention, which conditions are to be met by appropriate measures. The results are not very encouraging, survival being secured for only from a few days to six to eight months at most. A large mortality attends such operative palliative efforts.

Operations should not be considered when there exist signs of generalization or symptoms of serious hepatic and pancreatic insufficiency. In other cases an exploratory laparotomy will permit the determination of the lesions, the appreciation of their extent and the limits of operability. In a patient who presents a tumor apparently quite limited and of small extent, radical treatment might be attempted. Most frequently, however, the advanced condition of the lesions and especially the general state of the patient will oblige the surgeon to confine himself to palliative attempts or to close the abdomen without any operative manœuvres whatsoever. Practically those cancers alone are possible of extirpation which are localized in the gland itself but experience has shown that the invasion of the gland is always much more extensive than the primary examination would lead to suppose and that partial pancreatectomy is promptly followed by recidive in most cases. The proportion of cancers in which radical treatment is justifiable therefore is very small. The attempts at treatment by radium are still too few and recent to make a positive judgment practicable. A very extensive bibliography concludes the book.

The book as a whole with its 330 pages of text and many illustrative cuts produces a volume of great interest in which its subject receives thorough and judicial treatment. The extent of the bibliography which it is now possible to bring together upon the subject of cancer of the pancreas has become quite large and has evidently been thoroughly studied by the authors. The condition itself is one which for its successful management must be left to curative medical treatment when the happy time shall have arrived when such treatment for cancer shall have been devised.

LEWIS S. PILCHER.

TUMORS OF THE BREAST, THEIR PATHOLOGY, SYMPTOMS, DIAGNOSIS AND TREATMENT. By SIR G. LENTHAL-CHEATLE, F.R.C.S., of London and MAX CUTLER, M.D., of Chicago. Philadelphia, J. B. Lippincott Company, 1931.

This book, presenting 596 quarto pages and 466 illustrations, is encyclopædic in its character and may properly be claimed to present fully the present condition of knowledge as to its subject. To its composition the authors have brought the outcome of many years' study of normal and abnormal conditions of the breast, for which they have enjoyed unusual opportunities, both in extent and in character. Examination of its pages will show the critical surgeon that they embody fully the knowledge of the day with regard to the subjects treated.

Preliminary pages are devoted to the anatomy and physiology of the breast. This is followed by 100 pages devoted to benign neoplasia, after which comes, constituting the great mass of the book, the real object of its compilation: cancer, occupying more than 400 pages. The teachings of the book are based upon the premise, "Carcinoma is the presence of living, multiplying and invading epithelial cells in parts where they have no normal right to be." (Page 161.)

The book essentially is one of pathology and diagnosis. The subject of surgical treatment does not enter into the scope of the book. A chapter, however, is devoted to the radiation treatment of carcinoma of the breast. The book, as a whole, in the field to which it is devoted, will secure the approval of educated and progressive surgeons, and will take an important place as a sound book of reference.

L. S. P.

THE AMERICAN JOURNAL OF CANCER. Vol. XV, No. 1, January, 1932. Editor, FRANCIS CARTER WOOD. Large 8 vo.; pp. 561.

WITH its number of January, 1932, the Journal of Cancer Research announces that it will be continued under the caption of THE AMERICAN JOURNAL OF CANCER, remaining the official organ of the American Association for Cancer Research and the American Society for the Control of Cancer under the continued editorship of Dr. Francis Carter Wood with the coöperation of an editorial board which includes a large number of prominent surgeons and pathologists.

The occasion for the being of this journal was a want felt by the members of the associations named of a publication devoted to the more technical side of cancer investigation, one in which articles not readily acceptable to the current clinical journals might be published. The first number of this Cancer Journal appeared in January, 1916, and has continued to the present time. It is now still to be continued as a quarterly periodical, soliciting for publication manuscripts on all phases of cancer, experimental, clinical, statistical and educational. The present number, under its new name, consti-

tutes an imposing volume of nearly six hundred large, octavo pages, about one-half of them being devoted to clinical and pathological original reports and half to abstracts of articles from current literature.

That there is a place for such a journal is unquestionable. The interest in all phases of the cancer problem is universal and deep and the solution of the questions connected with it is of the highest importance. The present number of the ANNALS OF SURGERY is devoted entirely to subjects pertaining to this problem. The activities of organizations, both professional and lay, for research into its mysteries are widespread and continually increasing in importance. The cause and cure of cancer are two riddles that continually intrigue for their solution the deepest thought and the most constant and intelligent experimental research of which the human mind is capable. There is no question but what an important part in the solution of this riddle may be played by this AMERICAN JOURNAL OF CANCER, and as a collaborator in this field, we welcome it.

L. S. P.